THE 1952 YEAR BOOK *of* MEDICINE

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Departments *of the* Year Book *of* Medicine

Infections

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The Chest

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PUBLISHER'S NOTE

The dates appearing under the title of this YEAR BOOK indicate that journals received within that period have been reviewed by the editors in selecting the articles abstracted herein

INFECTIONS

PAUL B BEESON M.D

PART I

INFECTIONS

BASIC INVESTIGATIONS

Effect of Spermine on Tubercle Bacilli. Certain pathologic features of tuberculosis suggest that multiplication of tubercle bacilli in vivo is limited by mechanisms other than those of

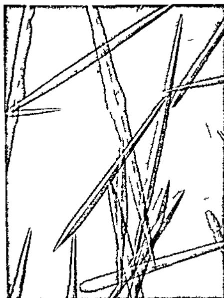


Fig 1 —Cry t l f p m ph ph t l t d f om t su d d f om × 57 (Cou t y f H h J G d D b R J J E pe Med 95 191 08 F b 1 1952)

conventional immune processes The great differences known to exist in the susceptibility of various species and organs to tuberculosis also suggest that nonimmune mechanisms are influential in determining the events of host parasite relation

known evidence that adrenalectomy definitely decreases resistance to infection Purpose of the present investigation was to relate the infectious activity of two bacterial species Staphylococcus aureus and Salmonella aertrycke to the role of the adrenal cortex in resistance to infection It was assumed that the strain of Staph aureus used contained an active spreading factor most likely hyaluronidase

Since protection was observed in mice after injection of adrenal cortical extract it seemed likely that part of this protection was due to inhibition of the bacterial spreading factor by the adrenal cortical steroids of the extract To prove this a suspension of Staph aureus in saline solution was mixed with an equal amount of adrenal cortical extract and this mixture was injected intradermally into normal and adrenalectomized mice The extract provided considerable protection as evidenced by development of smaller and less severe lesions than those in the control groups The protective effect was seen in both normal and adrenalectomized animals Dosage was considerably smaller than that used in previously reported experiments results paralleled closely the inhibition of the spreading phenomenon by adrenal cortical steroids as reported earlier

The investigations of Duran Reynolds and others have suggested that S aertrycke does not contain the enzyme hyaluronidase As this organism is highly infectious for mice it was chosen for the second series of studies Within 10 days all infected animal died Administration of adrenal cortical extract either aqueous or Lipo adrenal did not appear to affect the course of infection in normal animals although adrenalectomized ones were protected to some degree

It has been well established that the spreading factor is an important agent governing invasion of bacteria through the barrier provided by the ground substance of the mesenchyme Results of the present investigation indirectly support this conclusion The extreme sensitivity of the adrenalectomized animals to all type of infection as well as to many types of nonspecific stress makes it apparent that the relation between the adrenal hormones and hyaluronidase can be only one of several factors involved

[Except for the body of knowledge on antibodies and phagocytosis we know little about factors influencing host resistance and susceptibil

in this disease For example the guinea pig kidney is remarkably resistant to tuberculous infection even when the bacilli are injected directly into renal tissue Although it is usually assumed that anatomic characteristics play a large part in controlling resistance to infection it also appears possible that there are in certain animal tissues heretofore unrecognized substances which can interfere with the parasitic behavior of infective agents James G Hirsch and Rene J Dubos[1] (Rockefeller Inst) isolated an antimycobacterial substance from tissue extracts and studied its properties

This substance is capable of suppressing the growth of a variety of mycobacteria in vitro it was found to be equally active against virulent attenuated and avirulent variants of human and bovine tubercle bacilli but had little or no effect on saprophytic mycobacteria and on several non acid fast microorganisms under the conditions of the test The inhibitory activity on growth of tubercle bacilli was essentially independent of the size of the inoculum within the limits studied

By chemical purification and analysis the inhibitory material was identified as spermine an organic base widely distributed in animal tissues (Fig 1)

[A most interesting and provocative piece of work This pattern of investigation may be productive of further information since it is reasonable to assume that variations in susceptibility to infection may be related to definable constituents of certain tissues —Ed]

Adrenal Hyaluronidase Relation in Infection was investigated by Geo H Smith and Jeanette C Opsahl The study involved the effects of derivatives of the adrenal cortex on spreading of actual parasites in the host Spreading throughout tissues of particulate matter such as the carbon in India ink can be enhanced by hyaluronidase Many bacteria also spread from a localized focus and it has been shown that this spreading may be facilitated by hyaluronidase or a similar agent Since both adrenal cortical hormones and hyaluronidase are said to play important roles in processes of infection it seemed reasonable to suppose that the two systems might interact in some way Many individual studies have been made of the effects of cortical extracts or adrenalectomy relative to isolated disease pathology but results for the most part have been inconclusive except for the well

(1) J Exper Med 95 191 08 Feb 1 1952
(2) Yale J Biol & Med 23 361 369 Apr 1 1951

Weinstein[4] (Boston) attempted to determine by penicillin therapy whether antibacterial immunity was affected in the same manner as the antibodies for the soluble products of the organism

Results indicate that appearance of bacteriostatic antibody was related to the route of administration and quantity of penicillin Type specific antibacterial immunity did not develop in any who received 250 000 units of antibiotic intramuscularly The same dosage by mouth however permitted appearance of antibody in 21% A moderate difference in occurrence of antibacterial activity in the serum was also detected when 150 000 units of penicillin was given by different routes Nearly always when an antibacterial effect of the serum was demonstrable level of activity was much less than observed by Rothbard in untreated patients Findings suggest that penicillin not only may completely inhibit development of antibacterial immunity but may decrease quantity and shorten duration if the antibody appears Depression of antistreptococcic antibody production by penicillin is probably related to the rapid elimination of the infecting organisms Importance of the time of contact between the host and organism before treatment in development of immunity has previously been pointed out

Inhibition of development of bacteriostatic antibody by penicillin in patients with streptococcic infections probably is more important clinically than similar depression of antistreptolysin O antistreptokinase and antihyaluronidase The antibacterial antibody protects against reinvasion by a homologous serologic type the other antibodies probably play little or no role in defense against invasion by the organism Failure to develop type specific antibacterial antibody for the streptococcus after penicillin therapy increases risk of subsequent infection by homologous serologic types

[Although of interest this should not alter our current practice of adequate chemotherapy for all acute hemolytic streptococcic infections The choice is between greater susceptibility to another acute streptococcic infection or protection against the development of rheumatic fever (See discussion of preceding article and this YEAR BOOK p 107) There isn t much choice between them —Ed]

Mucoprotein Derived from Human Urine Which Reacts with Influenza Mumps and Newcastle Disease Viruses Pre

(4) Proc Soc Exp Biol & Med 78 160 163 October 1951

ity In the case of pyogenic infections it is obvious that ability of the organisms to permeate tissues must be a matter of great importance Studies such as this are beginning to throw a little light —Ed]

Experimental Determination of Hypersensitive Diathesis in Man is reported by William P Creger Sun Hak Choy and Lowell A Rantz[3] (Stanford Univ) It is well known that animals differ in their capacities to produce circulating anti bodies to a given antigenic stimulus Indirect evidence sug gests that man also differs in these capacities but there are no experimental data assembled to demonstrate significant population differences in antibody forming potential

Of 48 medical students given injections of standard com mercial influenza vaccine in 1948 19 were available two years later for testing with another antigen entirely unrelated to the vaccine previously used The antigen chosen was human blood of the heterologous group In two subjects there was a striking isoantibody response with peak levels of 2 000 and 5 000 They also reacted with abnormal vigor to immunization by antigens prepared from the viruses of influenza A and B by producing large amounts of both anti PR8 and anti Lee anti body

A small group of persons with diseases in which hyper sensitivity may play a role were tested by the mismatched blood technic A sharp isoantibody response occurred in one each with disseminated lupus erythematosus erythema no dosum and acquired hemolytic anemia and three with inactive rheumatic fever It is tentatively suggested that immunologic hyper reactivity is a characteristic of a few healthy persons and of those with certain diseases This attribute may be an important factor in pathogenesis of these disorders This hy pothesis is being further tested by a modification of the method described in which purified blood group substances are used instead of whole blood of heterologous group

[This is in accord with studies on the immune response following streptococcic infection i e among individuals who sustain streptococcic infections tho e in whom rheumatic fever develops generally exhibit the highest titers of antibodies to the streptococcus —Ed]

Streptococcic Bacteriostatic Antibody in Patients Treated with Penicillin. Administration of penicillin to patients with acute streptococcic pharyngitis suppresses formation of anti streptolysin O and antistreptokinase George Dankos and Louis

(3) J Imm 1 66 445-450 April 1951

Studies on Antibiotic Synergism and Antagonism Interference of Aureomycin, Chloramphenicol and Terramycin with Action of Streptomycin is reported by Ernest Jawetz Janet B Gunnison and R S Speck[6] (Univ of California) Availability of many satisfactory antimicrobial agents makes their use in combination tempting to the clinician After introduction of each new drug resistant bacteria are soon discovered and the physician resorts to combinations of drugs in hope of obtaining additive or synergistic effects In vitro and in vivo observations have disclosed certain combinations that had markedly increased effects over the single drugs Conversely experiments have shown that certain combinations of antibacterial drugs result in antagonism and diminished effect Previous reports have shown the ability of chloramphenicol aureomycin and terramycin to interefere with bactericidal and therapeutic effects of penicillin This indicates that penicillin was most active against rapidly multiplying bacteria and that the interfering drug slowed multiplication and thus blocked optimal penicillin action

Interference of aureomycin chloramphenicol and terramycin with action of streptomycin in vitro has been reported These drugs also can interfere in vitro with the bactericidal effect of streptomycin against Klebsiella pneumoniae Chloramphenicol interference is more notable than that of the other two agents As in the case of antagonism to penicillin the three drugs appear to interfere principally with the early bactericidal action of streptomycin this raises the question of a similar mechanism being involved

In experimental injections of mice to determine interference of antibiotics with the therapeutic effect of streptomycin it was found that streptomycin alone cured 30 50% more animals than when it was combined with chloramphenicol In multiple dose schedules antagonism was also definite Terramycin and aureomycin interfered less than did chloramphenicol

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(6) Am J M S 22 404 41 Oct b 1951

sumably by altering enzymatically the structure of the surface of red blood cells the influenza mumps and Newcastle disease viruses are capable of agglutinating chicken erythrocytes This hemagglutination can be inhibited by a variety of tissue suspensions *Igor Tamm and Frank L Horsfall Jr*[5] *(Rockefeller Inst)* report a study made in the belief that the interaction between these viruses and inhibitory components may be analogous to certain phases of the interaction between viruses and susceptible host cells Several attempts to isolate purify and identify inhibitory components have yielded substances of high activity but contaminated with noninhibitory substances However normal human urine on precipitation with sodium chloride and extraction with phosphate buffer yields a highly active inhibitor essentially free of proteins apparently a single homogeneous mucoprotein of a high molecular weight ($7 0 \times 10^6$) It consists of threadlike molecules which have axial ratios of about 100 and is specifically antigenic At equilibrium with the influenza virus the minimal amount of the substance capable of giving a demonstrable reaction with one hemagglutinating unit of the virus seems to be about 0 0003 μg In causing inhibition mucoprotein molecules appear to react with influenza viral particles in a proportion close to 1 1 The mucoprotein is altered by preparations of influenza virus and its capacity to react with these agents or others is lost The kinetics of this inactivation suggest enzymatic action No evidence was obtained that antibodies against urinary mucoproteins were capable of agglutinating either chick or human erythrocytes nor did they prevent infection of the chorioallantoic membrane with swine influenza virus

The evidence from this study and other work indicates that loss of ability of the mucoprotein to combine with influenza mumps and Newcastle disease viruses brought about by the action of enzymes associated with these agents is not due to extensive alteration in the molecular structure of the substance but is the result of the splitting off of a small portion of the molecule

[A promising lead toward the conquest of virus infections is being pursued here Knowledge of the means by which viruses unite with host cells may eventually provide ways of preventing or halting virus infections —Ed]

(5) J Expr Med 95 71 97 J ua y 1952

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(7) A M A Arch. Int. Med 88:489 494 October 1951

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When patients of all ages are considered the fatality rate (table) was much lower among those who received penicillin alone (30%) than among those given both antibiotics (79%)

FATALITY RATES IN PNEUMOCOCCIC MENINGITIS IN RELATION TO AGE

Age Y	P c L N T EATE		P CI L N STRE OMY T TE	
	N	D d	N	D d
Under 1	5	3 (60%)	0	
1 13	6	0	2	0
14-49	15	3 (20%)	6	5 (83%)
50 and over	17	7 (41%)	6	6 (100%)
All ages	43	13 (30%)	14	11 (79%)

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Fatality Rates in Pneumococcic Meningitis in Relation to Age

A e Y	P c l n T eate		P n l n Str tom n T t	
	N	D d	N	D d
Under 1	5	3 (60%)	0	
1 13	6	0	2	0
14-49	15	3 (20%)	6	5 (83%)
50 and over	17	7 (41%)	6	6 (100%)
All ages	43	13 (30%)	14	11 (,9%)

This difference is highly significant when tested by the Yates modification for small series of the chi square test *(x = 8 3)* The number of organisms in the initial smear of the centri fuged sediment of the cerebrospinal fluid was an important factor in prognosis More of the penicillin group than of the penicillin aureomycin group fell into the category with the

not to combine a bacteriostatic with a bactericidal agent of the penicillin type The bacteriostatic agents are capable of interfering with streptomycin action in a manner similar to that of penicillin although antagonism is less to the former than to the latter drug Penicillin exerts maximal antibacterial effects against actively multiplying organisms whereas in the action of streptomycin against K pneumoniae similar effects were noted on resting washed cell suspensions and multiplying cultures Bacteriostasis produced by the interfering drug has been a common denominator of the antagonistic effects observed Further no concentration of streptomycin has been shown to interfere with penicillin action or vice versa in the test tube or in experimental infections Penicillin streptomycin and perhaps bacitracin appear to be in one group and chloramphenicol aureomycin and terramycin in another Drugs of the second group may all interfere with action of drugs in the first Interference in vitro and in vivo is a unilateral phenomenon and may be observed only if the micro organism injected is susceptible to streptomycin If the bacterium is streptomycin resistant no interference can be observed A drug antagonism which can be demonstrated only in highly selected circumstances in experimental infections is unlikely to be important in treatment of clinical disease Interference of aureomycin and terramycin with streptomycin action is probably in this category

[This presents an important and disturbing clinical problem As reported in the next article there may be clinical situations in which one antibiotic interferes with the beneficial effect of another At present there is no reason to believe that penicillin and streptomycin cannot be given concurrently on the contrary they may act synergistically (see this YEAR BOOK p 26) The implication of the present authors that neither penicillin nor streptomycin should ever be given with aureomycin terramycin or chloramphenicol may not be justified Excellent experimental and clinical results have been obtained in brucellosis with a combination of aureomycin and streptomycin —Ed]

Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin Plus Aureomycin Studies Including Observations on Apparent Antagonism between Penicillin and Aureomycin Mark H Lepper and Harry F Dowling[7] (Chicago) point out that before sulfonamides were used pneumococcic meningitis was usually fatal An era of more successful therapy was started with the advent of penicillin

(7) A M A Arch Int M d 88 489 494 October 1951

about two weeks before onset and many had had severe diarrhea soon after taking the drugs Proctologic examination usually revealed perianal erythema with thickening and ex coriation of the perianal skin with or without multiple super ficial fissures at the margins of the anal aperture These changes were like those of idiopathic pruritus ani and chronic anal fissures which occur in the midline and penetrate more deeply causing rolled edges and sentinel piles In a few instances examination also disclosed ulcerative proctitis ulcerative colitis and perianal abscess In 100 patients the symptom complex appeared oftener in males in the ratio of 2 1 Aureomycin was the commonest offending drug and chloramphenicol caused the fewest complications There was no relation of severity of symptoms to amount of drug taken or period of time used Some of the severest complications were noted when an exceedingly small amount of drug was given

The condition was extremely resistant to treatment some times continuing to be severe for six to eight months despite active therapy Fungicidal ointments and powders were used for the pruritus condition local analgesic ointments for pain bleeding and superficial fissures and scarlet red ointment to promote healing Pathogenesis is undetermined Behrman be lieves that the normal intestinal flora is destroyed leaving the yeasts in relatively excessive numbers and once the restrain ing presence of the other organisms is removed a typical monilial infection develops The physician must exercise great caution in determining the efficacy of therapy with the drugs under discussion Often the anorectal complications following use of these antibiotics are far severer than the diseases for which they are used These drugs should not be given without specific indication for none is completely innocuous

[Amen!—Ed]

Virulence Enhancing Activities of Aureomycin on Candida Albicans Because of the frequently noted proliferation of fungus like organisms notably C albicans in the oral cavity intestinal tract etc and extension to invasive and disseminated disease in patients treated with the various antibiotics the Council on Pharmacy and Chemistry of the American Medical Association called attention to this danger It was suggested

poorest prognosis (four or more pneumococci per oil immersion field) Another prognostic factor the status of sensorium on admission revealed that the penicillin group contained a higher percentage of patients in the category which offered the poorest prognosis since 35% were comatose on admission as compared with 14% of patients in the penicillin aureomycin group Delay in initiation of treatment is an important factor in increasing the death rate in pneumococcic meningitis Fatality rates among patients given aureomycin and penicillin were higher however regardless of the time therapy was started

There are several possible explanations for the fact that patients treated with penicillin alone recovered more rapidly (1) The groups may not be comparable However in regard to age number of pneumococci in the cerebrospinal fluid presence or absence of coma purulent complications or underlying diseases and duration of disease before therapy little difference was found and results of penicillin therapy were superior in every situation in which comparison was made (2) Aureomycin in the doses used may be toxic particularly to the liver and so contribute to death As no toxic effects were noted it is not felt that the unfavorable results in the penicillin aureomycin group were due to aureomycin toxicity The most likely explanation is that aureomycin and penicillin are antagonistic when combined since results suggest that in addition to the evident interference with penicillin activity by aureomycin penicillin interferes with the antibacterial effects of aureomycin

[This is the first impressive clinical report of an antagonistic clinical effect of aureomycin and penicillin One wonders whether the result obtained in these cases is related to the peculiar susceptibility of the meninges to infection Similar findings have not yet been encountered in pneumococcic pneumonia —Ed]

Anorectal Complications of Aureomycin, Terramycin and Chloromycetin[8] **Therapy** in some instances have been severe enough to require surgery In a year Sylvan D Manheim[8] (New York City) treated an increasing number of patients presenting an almost identical symptom pattern who complained of perianal itching associated with pain burning sensation and bleeding on defecation All gave history of oral ingestion of aureomycin terramycin or chloramphenicol

(8) New York J Med 51 59 60 Dec 1 1951

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(1) Surg Gynec & Obst 94 401 425 April 1952

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all results of therapy were favorable in 78% of patients Results were favorable in 91% of those given no previous treatment and in 72% of those treated unsuccessfully with penicillin and/or other agents

[The renal toxicity reported here is less serious than was encountered in earlier trials Bacitracin should certainly be considered when penicillin cannot be used but few physicians would yet agree that it may be the drug of choice —Ed]

Treatment of Chronic Shigella Infection in Children with Oral Polymyxins Daniel Lieberman and Ernest Jawetz (Univ of California) used these agents because they so admirably meet the requirements for the ideal drug to control this disease (1) high bactericidal activity preventing development of resistant mutants (2) stability on oral administration (3) high therapeutic concentrations on intestinal surfaces and (4) lack of local or systemic side effects Polymyxin B and E are highly bactericidal for shigella organisms in vitro are stable and show no significant intestinal absorption when taken orally No blood levels can be detected after daily doses up to 400 mg/kg Most agents lack one or more of these characteristics and have limited effectiveness against shigella organisms which are largely confined to the intestinal mucosa surfaces Invasion and widespread dissemination are rare whereas chronic superficial infection is a common sequel of acute infection

A study was made among institutionalized mentally defective children Epidemiologic control of the disease in an institution depends largely on eradication of carriers and other chronic shedders Control studies using conventional chemotherapeutic measures revealed response in 93% of 116 fresh but only 63% of 78 chronic infections Polymyxin was given 23 children with chronic infections caused by Shigella paradysenteriae which were resistant to other therapy The drug was supplied as a white amorphous material in vials of 50 or 100 mg It was dissolved in water to give a concentration of 10 mg/cc and vanillin added to disguise the taste Total daily dose of 15 20 mg/kg was divided in three portions and given for 10 days No toxic side effects were noted Cure rate was 87% demonstrating the greater value of polymyxin in this type of infection

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Subacute Bacterial Endocarditis is discussed by J E Cates and Ronald V Christie[3] (St Bartholomew's Hosp London) In February 1945 the Penicillin Trials Committee of the Medical Research Council appointed 14 centers in Great Britain to study the value of penicillin in subacute bacterial endocarditis The effects of age sex various under lying heart lesions and other factors were also studied By January 1949 442 patients had been treated 408 had posi tive blood cultures before treatment was begun and 34 did not but showed all the other signs of the disease Patients with acute bacterial endocarditis were not included

The infecting organism was Streptococcus viridans in 87% and a nonhemolytic streptococcus in 7% of the patients There was relapse in 65 patients with *Str viridans infection* and increased resistance to penicillin in 15 being 3 fold or less in 7 patients 4 to 10 fold in 7 and 160 fold in 1 A double in fection was found in two patients in a third three different organisms were grown from the blood on different occasions but there was some doubt whether all three came from the heart It cannot be ascertained whether a second attack of bac terial endocarditis is a relapse or a reinfection unless the sec ond organism differs from the first In three cases blood cul tures before treatment grew Str viridans alone but other organisms (Pseudomonas pyocyanea Str faecalis Bacterium coli) appeared later and killed the patients After being appar ently cured for 8 months to 5½ years 14 other patients had a second attack In three the second organism differed from the first in four there was clinical or bacteriologic evidence that a new infection might have caused the second attack in seven the first and second organisms were similar but their characteristics on culture were not closely compared

In early trials with penicillin patients were divided into three groups with all given a total of 5 000 000 units but varied duration of treatment (1) 1 000 000 units daily for 5 days (2) 500 000 daily for 10 days and (3) 250 000 daily for 20 days Treatment failed to eliminate infection in 83% of

(3) Q rt J M d 20 93 130 Ap l 1951

group 1 50% of group 2 and 22% of group 3 indicating that within the limit of this dosage duration of treatment was more important than total amount given Therefore it was recommended that patients be given as a minimum 2 000 000 units daily for four to six weeks however sensitive the infecting organism (Christie 1949) Combined use of penicillin and streptomycin was first suggested by Hunter and its value has been confirmed by Robbins and Tompsett In the present trials this was the preferred treatment

In 87 patients the first course of penicillin failed to eliminate the infection and blood culture either remained positive during treatment or became positive again within six months The interval between end of treatment and relapse was rarely more than a month and in only 3% of relapses was it over 2 months Risk of a delayed relapse or reinfection after six months of apparent cure is 2% per annum

Major arterial embolism was diagnosed during life in 145 patients (35%) Although 81 died death was due to embolism in only 17 and partly due to it in another 9 It is clear that the risk of major embolus remained for several months after apparent cure and that embolus occurring in convalescence was often a more serious complication than one occurring during treatment possibly because as a vegetation heals fragments detached from it tend to be firmer and larger Cerebral emboli occurred in 70 patients 3 having two separate attacks Cerebral embolism therefore affected 17% of the patients and contributed to 10% of the deaths in addition to maiming some of the patients who survived Coronary embolism was diagnosed during life in eight patients contributed to death in six of these and was found post mortem in another eight Pulmonary embolism was found in 51 patients it was diagnosed during life in 49 and discovered post mortem in 2 Hemorrhage from rupture of a mycotic aneurysm was the main cause of death in 17 patients and partly the cause in 3 others Hemorrhage was cerebral in 16 mesenteric in 2 from the femoral artery in 1 and into the pericardium in 1 Arrhythmia was noted in 20 patients 18 had auricular fibrillation 1 paroxysmal auricular tachycardia and 1 varying heart block As McDonald (1946) has shown the two conditions are found together more often than is generally

recognized and presence of fibrillation does not preclude diagnosis of bacterial endocarditis

Changes in heart murmurs during and after treatment were relatively uncommon being observed in about 15% of patients True incidence of active rheumatic carditis was not known because detailed histologic study of the heart muscle was not included in the investigation Separate studies made in Belfast (MacIllwaine 1947) and Edinburgh (Matthew and Gilchrist 1948-49) revealed that the condition was common though sometimes unsuspected during life Uremia was the cause of death in 18 patients 10 of whom also had heart failure The latter was the commonest cause of death Of 195 fatal cases in this series it was the main cause in 104 (53%) and a subsidiary cause in another 19 (10%) Other causes of death were arterial embolism (13%) hemorrhage (10%) uremia (9%) rheumatic fever (2%) pulmonary embolism (2%) pneumonia (2%) and other complications (14%)

Presence of heart failure before treatment had a profound effect on prognosis Of those with no heart failure 37% died of those with moderate heart failure 70% of those with severe heart failure 97% Development of heart failure during treatment was also a bad sign Of 109 patients without heart failure before treatment began it developed during treatment in 16 of these 13 (81%) died Heart failure did not develop in the remaining 93 and of these only 17 (18%) died Duration of infection appeared to be significant Of the patients recently infected 36% died of those infected for 10-19 weeks 50% of those infected for 20 or more weeks 62% The good prognosis in congenital heart disease was partly related to the fact that heart failure and a bad or emaciated nutritional state were less common in this type of lesion than in acquired heart disease Clinically the underlying heart lesion was thought to have been acquired in 32 of the patients with bacterial endocarditis

From these observations it seemed that most of the patients with negative blood cultures were similar to the abacteremic ones described by Keefer rather than to those in the bacteria free stage of Libman and Friedberg That infection is usually present in the vegetations although the organism cannot be grown in blood culture is strongly suggested by the postmortem findings and by response of fever to

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In 87 patients the first course of penicillin failed to eliminate the *infection and blood culture either remained* positive during treatment or became positive again within six months The interval between end of treatment and relapse was rarely *more than a month and in only 3% of* relapses was it over 2 months Risk of a delayed relapse or reinfection *after six months of apparent cure is 2%* per annum

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explained on the basis of elimination by streptomycin of members of the bacterial population which survive exposure to but are partially inhibited by penicillin Thus although the penicillin concentration of the body fluids well exceeds the minimal inhibitory concentration for the infecting organism (as determined by the usual test) so that many of the bacteria die some remain viable and can resume multiplication after penicillin is stopped Presence of streptomycin in the body simultaneously with penicillin results in death of these persisting members of the bacterial population and thus in complete eradication of the parasites so that relapse cannot occur

[A very significant contribution Even when laboratory tests indicate that an enterococcus (Str faecalis) is relatively resistant to penicillin and streptomycin individually therapy with both agents may be life saving —Ed]

Treatment of Subacute Bacterial Endocarditis with Aureomycin Although penicillin is effective in most cases an antibiotic is needed which is potent when given orally and possesses a wider antibacterial range Charles E Friedberg[9] (Mount Sinai Hosp New York City) therefore treated 11 patients with aureomycin All had rheumatic cardiovalvular disease and unexplained fever for at least 2½ weeks Positive blood cultures were obtained from eight patients at least twice and the clinical picture was highly suggestive in the remaining three

METHOD —Therapy was begun orally At least 4 and preferably 6 Gm was given daily in divided doses every six hours but the schedule was often modified to smaller doses at four or three hour intervals Aureomycin was continued for five to eight weeks if clinical response was satisfactory If however fever persisted or recurred or if blood cultures remained or became positive it was discontinued and penicillin or other antibiotic therapy was instituted

Often aureomycin promptly eliminated fever and sterilized the blood Nevertheless despite these improvements lasting as long as eight weeks over all clinical improvement and recovery usually did not result Recovery followed in four patients (44%) two with positive blood cultures Five who had positive cultures subsequently recovered on other antibiotic therapy four on penicillin and one on combined therapy with various agents Two of the patients treated successfully with aureomycin had failed to respond to penicillin previously

(9) J A M A 148 98 103 Jan 1 1952

penicillin Results achieved by Loewe and Eiber who gave larger doses of penicillin and by Wilcox who used streptomycin support this view

[This is an important collection of facts about subacute bacterial endocarditis as it occurs today Data on age sex incidence valves affected etc are not included in the abstract The over all death rate is a little higher than has been reported from several individual clinics (with smaller numbers of cases) The tendency now is to use even larger doses of penicillin —Ed]

Treatment of Enterococcic Endocarditis and Bacteremia Results of Combined Therapy with Penicillin and Streptomycin In about 5 10% of cases of subacute streptococcic endocarditis there is high resistance to penicillin Most are due to enterococci a subdivision of the genus streptococcus Occasionally *arrest has been achieved with great amounts* given for long periods These organisms have also resisted streptomycin therapy Since 1947 however concurrent penicillin and streptomycin therapy has been used successfully in patients with enterococcic endocarditis William C Robbins and Ralph Tompsett[4] (New York Hosp Cornell Med Center) discuss their experience with six patients with bacteriologically proved enterococcic disease The organisms isolated from each gave a positive reaction with Lancefield group D antiserum Concurrently 500 000 units of crystalline penicillin was given intramuscularly every two hours and 0 5 Gm streptomycin or dihydrostreptomycin intramuscularly four times daily for a total of 6 000 000 units of penicillin and 2 Gm streptomycin *each daily Whenever possible the regimen was continued for* 28-42 days Although the clinical picture resembles that of Streptococcus viridans endocarditis there is some differentiation in age distribution in males and females since the enterococci are commonly present in the gastrointestinal tract and are frequent invaders of the genitourinary tract Thus males are most apt to become infected in relation to operation on the prostate whereas infection in females is often related to abortions or pregnancy or in a younger age period Also enterococcic endocarditis is more prone to gross abscess formation *especially in the spleen during course of the* disease

The excellent response of human enterococcic endocarditis to concurrent administration of these two drugs might be

(4) Am J Med 10 78 99 M h 1951

Development of severe heart failure was of course attributable to the rapidly progressing aortic insufficiency

Since it is apparent that in acute endocarditis aortic valvular dysfunction associated with development of progressive heart failure is usually a direct result of early cusp destruction prompt control of the endocardial infection is of greatest urgency It is highly important to bear in mind the possibility of endocarditis as a complication during pneumonia If endocardial infection is suspected vigorous antibiotic therapy must be instituted at once to minimize the destructive process The intensive treatment must be continued for a relatively long period probably a minimum of six weeks It was noted in these patients that inadequate therapy may be repressive but not curative

[The occurrence of meningitis or bacteremia after the first week of pneumonia should suggest the possibility of endocarditis Since acute bacterial endocarditis can develop on a previously normal valve there may not be a heart murmur —Ed]

TREATMENT OF PNEUMONIA

Treatment of Clinical Pneumonia with Antibiotics Report by Subcommittee of Antibiotics Clinical Trials (Nontuberculous) Committee of the Medical Research Council[7] Because of the effectiveness of aureomycin and chloramphenicol on a wide range of etiologic agents including certain bacteria rickettsias and viruses not susceptible to penicillin or sulfonamides a trial was begun to find out which antibiotic was best to use when a clinical diagnosis of pneumonia was made The trial began in February 1950 and by April 1951 267 patients had been observed there were twice as many men as women The series was made up of adults admitted with the clinical diagnosis of pneumonia often confirmed by x ray If the initial diagnosis was proved incorrect the patient was excluded By random selection patients were treated by one of three methods (1) aureomycin in initial dose of 2 Gm followed by 1 Gm every 6 hours until the temperature remained normal for 24 hours after which 0 5 Gm was given every 6 hours for individualized periods (2) chloramphenicol in a similar regimen and (3) standard treatment with

(7) B M J 2 1361 1365 D 8 1951

The mechanism of cure was particularly obscure in one patient with endocarditis due to Streptococcus faecalis She failed to respond to large doses of penicillin and to aureo mycin and relapsed promptly after clinical and bacteriologic arrest during chloramphenicol therapy Since the causative organism was especially sensitive to terramycin, huge doses (12 15 Gm daily) were given for eight weeks during which she had no fever and blood cultures were negative Neverthe less she relapsed promptly after the antibiotic was discon tinued These observations indicate that chloramphenicol terramycin and aureomycin are usually bacteriostatic and not bactericidal in nonhemolytic streptococcic endocarditis

Penicillin intramuscularly or intravenously remains the preferred drug Recovery of two patients on aureomycin therapy alone after penicillin had failed signifies however that aureomycin may be a useful therapeutic supplement Its use should also be considered in bacterial endocarditis caused by penicillin resistant micro organisms other than nonhemolytic streptococci

[Results with the wide pectrum antibiotics in this disease have been disappointing presumably because they are not bactericidal They should be used only as a last resort when penicillin has proved to be of no value—Ed]

Acute Endocarditis as Complication in Bacterial Pneu monia In four cases studied Emanuel Applebaum Michael S Bruno and Elliot Hochstein[6] (New York Univ) were im pressed by the delay in diagnosis of the complication and by certain striking clinical and pathologic changes Since early recognition of an endocardial lesion during pneumonia is often difficult the essential criteria for diagnosis must be emphasized These include an endocardial murmur or mur murs particularly if diastolic evidence of impaired myo cardial function roentgen changes in size and contour of the heart pre ence of embolic phenomena persistence or recurrence of fever despite improvement in the primary dis ease and persistence of positive blood cultures However absence of embolic phenomena does not militate against diagnosis of endocarditis

In each case autopsy revealed endocardial infection of the aortic valve associated with dynamic aortic regurgitation

(6) J A M A 148 93 98 J 12 195

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penicillin and/or sulfonamides Only eight received the latter alone

On hospitalization a specimen of sputum was cultured on blood agar and also injected intraperitoneally into a mouse If sputum was not obtained a nasopharyngeal swab was examined Blood culture was made immediately and a white blood cell count as soon as possible Specimens of serum for virus studies were obtained on admission about the 15th day of the pneumonia and when possible about the 2?th day

TABLE 1—ETIOLOGIC AGENT OF PNEUMONIA IN 267 PATIENTS

	Au eo m c	C lor m ph n o	Stan	A l Tr at ments
Pneumococcus*	59 (69 [illegible])	76 (79%)	61 (?1%)	190 (?3 [illegible])
Staphylococcus	1	1	6	8
Streptococcus	0	1	1	2
Friedlander s bacillus	2	1	0	3
Hemophilus influenzae	1	0	0	1
Probably bacterial	14 (16%)	12 (13%)	13 (15%)	39 (15%)
Pneumonia with cold hemagglutinins	1	2	1	4
Undetermined origin	7	3	4	14
Pos titers for influenza A or B (included in foregoing groups)	9 (11%)	22 (23%)	16 (19%)	47 (18%)
Total patients	85	96	86	267

*Th ty s [illegible] (19%) pat [illegible] t w th pn [illegible] m [illegible] c [illegible] p e m n [illegible] had po t [illegible] blood cult [illegible] d t b t on mong the t eatm nt gr [illegible] p was app o m t ly eq al

N B—Alth gh [illegible] d o t [illegible] ll ases [illegible] ne wa d gn s [illegible] p tt [illegible] Q fe [illegible] w [illegible] th [illegible] g h a t gglut n [illegible] titer to St MG [illegible] abse [illegible] of a [illegible] ld aggl t [illegible] r a me sp [illegible] h [illegible] t olog c age it

The treatment groups were reasonably comparable with regard to etiology except that there were more patients with influenza in the chloramphenicol group and of patients with staphylococcic pneumonia in the standard group (Table 1) It is interesting that 73% of the patients had pneumococcic pneumonia All three treatment plans gave similar results as judged by the time taken for the temperature to fall physical signs to disappear x rays to become clear and the patient to get up and to be discharged The numbers of deaths and relapses were similar in each treatment group as were the numbers of patients for whom a change of treatment was thought necessary (Table 2) There were 19 deaths 7 in patients under age 60 and 12 in patients age 60 or over all

but 2 had chronic bronchitis and 1 of these had had bronchitis for two months before onset of pneumonia Of the five deaths among the 86 patients in the standard group four

TABLE 2—RESULTS OF TREATMENT

	Aureomycin	Chloramphenicol	Standard
Total patients	85	96	86
Deaths	7	7	5
Relapses (no of patients)	8	3	4
Change of drug or addition to treatment (no of patients)	5	8	3
Patients 'failing' on specified treatment (i e appearing in one or more of foregoing categories)	15	14	12

TABLE 3—COMPLICATION OF PNEUMONIA OCCURRING UNDER TREATMENT

	Aureomycin	Chloramphenicol	Standard
Sterile pleural effusion	4	3	2
Empyema	2*	0	1
Lung abscess	1*	1	0
Pneumothorax	0	1	0
Cardiac failure	1	2	0
Arthritis	1	0	1
	9	7	4

* O[illegible] lung abscess [illegible] empyema [illegible]

TABLE 4—DRUG TOXICITY

	Aureomycin	Chloramphenicol	Standard
Total patients	85	96	86
Total patients with symptoms of toxicity	(31 8%)	1 (19%)	5 (5 8%)
Nausea — mild	10	2	0
Nausea — severe	1	0	0
Vomiting — mild	6	1	0
Vomiting — severe	1	1	0
Diarrhea — mild	7	5	0
Diarrhea — severe	0	0	0
Rashes	4	2	1
Red or sore mouth or tongue	5	9	4
Black tongue	2	2	0
Rectal irritation	1	0	0
Vaginitis	0	1	0
Drug fever	2	0	0
Mental symptoms	0	4	0

occurred in 22 treated chiefly with oral penicillin Complications and evidences of toxicity are listed in Tables 3 and 4

The differences in the treatment groups are not statistically

significant The figures suggest that penicillin is at least as good as the other antibiotics and when cost is considered it is 10½ times as expensive to use aureomycin and over 9 times as expensive to use chloramphenicol In a choice of aureomycin chloramphenicol and penicillin, it therefore seems proper to recommend penicillin by injection as initial treatment There are some indications that it may even be better than the other antibiotics Since only eight patients received sulfonamides alone no comparison can be made of their value

Comparison of Aureomycin and Chloramphenicol in Treatment of Bacterial Pneumonia Pneumococcic pneumonia responds to aureomycin much as it does to penicillin Much less is known concerning the effectiveness of chloramphenicol

William M M Kirby Jean C Michel Daniel H Coleman James W Haviland and Donal R Sparkman[8] (King County Hosp Seattle) treated 50 patients with aureomycin and 50 with chloramphenicol The plan was to give aureomycin and chloramphenicol to alternate patients 1 Gm being administered daily in a single dose but several exceptions were made In other respects the two groups were quite similar Pneumococcic pneumonia was diagnosed in 76 patients and blood cultures were positive for pneumococci in 15 2 had pneu

COMPLICATIONS AND DEATHS

	AUREOMYCIN GROUP	CHLORAMPHENICOL GROUP
Complications		
Sterile effusion	1	3
Relapse	0	1
Delayed resolution	3	2
Collapsed lobe	1	1
Meningitis	1	1
Empyema	1	0
Thrombophlebitis	1	0
Total	8	8
Deaths		
Pneumococcic pneumonia (type III)	1	0
Pneumonia (pneumococcus type XVIII and Friedlander s bacillus)	0	1
Empyema	1	0
Multiple sclerosis aspiration pneumonia	1	0
Cardiac failure	1	0
Cerebrovascular accident	1	0
Multiple myeloma	0	1
Total	5	2

(8) J A M A 147 110 115 Sept 8 1951

monia caused by Friedlander s bacillus 2 by Escherichia coli and 1 by Hemophilus influenzae in 19 etiology was unknown

Favorable results were obtained in adults with both drugs Prompt response to aureomycin was similar to that previously described by others From a comparative standpoint superiority could not be claimed for either agent Results appeared to justify the conclusion that 1 Gm daily is adequate for treatment of many but possibly not all patients with bacterial pneumonia

Complications were similar in incidence and severity to those observed in patients treated with penicillin and in previous studies with aureomycin (see table) Sterile pleural effusions were noted in four patients and there were two pneumococcic empyemas Preparations of aureomycin and chloramphenicol suitable for intrapleural instillation are not yet available and therefore empyemas when they appear must be treated with penicillin The two patients with pneumococcic meningitis are of special interest One with meningitis on hospitalization showed some improvement in cerebrospinal fluid as a result of intensive aureomycin therapy but cultures remained positive Three days later penicillin was begun and the fluid was sterile in 24 hours In the other patient signs and symptoms developed 18 hours after chloramphenicol therapy was started Thus aureomycin and chloramphenicol are probably inferior to penicillin in treatment of pneumococcic meningitis

[Two points in this study were surprising to me (1) that such satisfactory results could be obtained with administration of only 1 Gm once a day (2) that chloramphenicol was as effective as aureomycin in pneumococcic infections —Ed]

Terramycin Therapy of Pneumonia Clinical and Bacteriologic Studies in 91 Cases George G Jackson Thomas H Haight Edward H Kass C Ray Womack Thomas M Gocke and Maxwell Finland[9] (Boston) report results of terramycin treatment in 68 patients with pneumococcic pneumonia and 23 others with pneumonias of varying etiology This broad spectrum antibiotic was usually given in doses of 0 5 Gm orally every four hours after a single starting dose of 1 Gm to about two thirds of the first group and about half of the second Average total dose for patients with pneumococcic

(9) A I M d 35 1175 120 D mbe 1951

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Multiple sclerosis aspiration pneumonia	1	0
Cardiac failure	1	0
Cerebrovascular accident	1	0
Multiple myeloma	0	1
Total	5	2

(8) J A M A 147 110 115 Sept 8 1951

the first three days after terramycin was started and none had fever more than a week Staphylococcic superinfection occurred in five four had enteritis and one urinary tract in volvement Diarrhea with monilia in the stools and develop ment of a rectovesical fistula were features in the only fatal case in this group Severe vomiting diarrhea and uremia also developed

The outstanding and probably the most important fea tures of this series are the frequency and rapidity with which pathogenic strains of Staph aureus almost all of them highly resistant to terramycin emerged and replaced the flora of the

UNTOWARD EFFECTS ATTRIBUTABLE TO TERRAMYCIN AMONG 91 PATIENTS WITH PNEUMONIA

T I	No PA NTS	%
None	38	4_
Nausea only	4	4
Vomiting and nausea	12*	13
Diarrhea vomiting and nausea	17†	19
Staph aureu predominant in fecal culture (and vomitus in 2 cases)	7	9
D arrhea without vomiting	20‡	22
Staph aureus predominant in fecal culture	5	6
Monilia predominant in stool	1§	1
Drug rash	1	1
Stomatitis and glossitis	2	2
Nitrogen retention	4	4
Severity necessitated reduction in dose	8	9
Severity necessitated changing to another agent (aureomycin or penicillin)	10	11

I lud p t t w th t og t t
†I l d th p t t w th drug h d th w th t g n t t
‡I lud th tw pat ts w th t m t t a d gl t
§Bl dy d h de l p d n th pat t d te m lly fec l fi t la d t g t t

sputum during treatment The frequent tendency of terra mycin to produce enteric irritation and the superimposition of staphylococcic diarrheas are evidences of the significance of staphylococci in this series and of the importance of terra mycin therapy in initiating and sustaining infections with these organisms These infections occurred in the more seri ously ill patients and increased morbidity and mortality These untoward results of terramycin therapy have not been limited to patients with pneumonia nor have these serious effects been confined entirely to therapy with terramycin (table) In five of the seven fatal cases the toxic effects of terramycin on the gastrointestinal tract may have contributed in a large measure

pneumonia was 19 Gm in 6 6 days and for those with other types of pneumonia 15 7 Gm in 5 5 days

Pneumococci were cleared rapidly from the sputum Thus on the first day after therapy was begun organisms were demonstrable in 40 of 61 patients studied whereas on the next day only 16 of 58 had positive cultures However other organisms such as Staphylococcus aureus monilia and coliform organisms became increasingly abundant under therapy and in most cases in which Staph aureus first appeared in large numbers these organisms persisted in the convalescent observation period The immediate effect of terramycin on fever and toxemia and other manifestations of active acute infection was generally favorable and prompt in most cases of pneumococcic pneumonia Complete subsidence of fever and symptomatic recovery occurred less regularly and more slowly Thus among the patients who recovered 24 had some fever for five days or more and half of these continued to have fever for more than a week after terramycin was started

The commonest complication of the original pulmonary infection was pleural effusion which was usually sterile Six had atelectasis and resolution was delayed for over four weeks in five The most frequent and significant complications however were superinfections with hemolytic and coagulase positive strain of Staph aureus Four had pulmonary involvement one of whom also had staphylococcic otitis media and conjunctivitis Severe diarrhea developed in nine Stool cultures yielded Staph aureus as the only or the predominant organism Diarrhea cleared on cessation of therapy in some but persisted several days in others

All aspects considered the authors classified results as *excellent good or moderately good in 72% of the 68 patients* with pneumococcic pneumonia There were six deaths in this group One patient was critically ill on admission and died soon after the initial (intravenous) dose of terramycin This dose was apparently sufficient as culture of blood drawn at autopsy showed a change from positive to negative In four cases severe superinfection in the lungs with staphylococci was held responsible for the fatal outcome

On the whole results in the patients with the other types of pneumonia were better Only 3 of the 22 who recovered failed to have temperature decrease to 100 F or less within

the first three days after terramycin was started and none had fever more than a week Staphylococcic superinfection occurred in five four had enteritis and one urinary tract involvement Diarrhea with monilia in the stools and development of a rectovesical fistula were features in the only fatal case in this group Severe vomiting diarrhea and uremia also developed

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Vomiting and nausea	1?*		13	
Diarrhea vomiting and nausea	17†		19	
Staph aureus predominant in fecal culture (and vomitus in 2 cases)		7		9
Diarrhea without vomiting	20‡		22	
Staph aureu predominant in fecal culture		5		6
Monilia predominant in stool		1§		1
Drug rash	1		1	
Stomatitis and glossitis	2		2	
Nitrogen retention	4		4	
Severity necessitated reduction in dose	8		9	
Severity necessitated changing to another agent (aureomycin or penicillin)	10		11	

I l d p t t w th n t og t t n
†I l d th p t ent w th d ug ra h d th w th t g n t t
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to the outcome In addition staphylococci played an important pathogenic role in the lungs in four of these cases

[A chilling report on terramycin Penicillin is still very good medicine —Ed]

Antibiotic Therapy of Friedlander Pneumonia Little information is available concerning effectiveness of the newer antibiotics in the therapy of the disease The causative organism Klebsiella pneumoniae is highly susceptible to aureomycin chloramphenicol and terramycin in vitro and in animals One report described a dramatic response to aureomycin in a patient who had shown no improvement after a week of penicillin therapy and another described similar success with aureomycin in three other patients William M M Kirby and Daniel H Coleman[1] (Seattle) report on 11 patients with Friedlander pneumonia treated with sulfonamides streptomycin aureomycin and chloramphenicol

The disease occurs predominantly in males ordinarily in a ratio 4 1 nine of the author s patients were male The predilection of the Friedlander bacillus for alcoholics is well known and eight of these patients were chronic alcoholics X ray films of five patients showed dense consolidation of pulmonary tissue and bulging of interlobar septa which is virtually diagnostic In vitro studies of nine strains of K pneumoniae isolated indicated that all but one were susceptible generally to the same degree to aureomycin chloramphenicol and terramycin Of six patients who died four had overwhelming infections and died within 16 hours despite intensive chemotherapy One died of lower nephron nephrosis and one had a mixed infection with death caused by Friedlander s bacillus empyema Four had positive blood cultures whereas only one who survived was bacteremic The generally poor physical condition of persons who contract Friedlander pneumonia and their frequent delay in seeking care probably contribute to continued high mortality rates Patients in relatively good physical condition who begin treatment early respond remarkably well

Aureomycin and chloramphenicol are therefore probably comparable to streptomycin in Friedlander pneumonia therapy At least it appears safe to use these antibiotics When more studies are made various regimens can be compared

(1) Am J Med 11 179 187 Aug 1951

Diphtheria Present Day Problem is discussed by Henry Brainerd and Henry B Bruyn (Univ of California) Diphtheria has become even more common in recent years particularly in older age groups in which mortality and complications are increasingly important Of 273 patients studied in the isolation division of the San Francisco Hospital during 1942 50 65% were males Mortality rate for males over the period was 20 2% and for females 17 8% Average hospitalization for patients who died was 10 days and for those who recovered 25 48 days All but one patient had diphtheritic infection of the respiratory tract one had cutaneous infection as the only manifestation and nine had skin involvement in addition to a lesion of the respiratory system Though 75 patients had laryngeal diphtheria only 12 had lesions of the larynx in the absence of pharyngeal diphtheria In 94 1% pharyngeal diphtheria was found

Myocarditis obstruction of the respiratory tract and neuritis were the most noted complications of diphtheria Myocarditis occurred in 100 patients (36 6%) 36 died Average time of appearance after onset of infection was 9 8 days with a range of 2-47 days In more severe cases anginal and abdominal pain syncope pallor vomiting hypotension arrhythmia deterioration in quality of the apical first heart sound gallop rhythm and murmur were noted Severe obstruction of the respiratory tract occurred only in patients with involvement of the larynx sometimes in association with diphtheria of trachea and bronchi Of 40 patients with severe degrees of obstruction 26 (65%) died Of 44 patients with neuritis 6 (13 6%) died In 16 cranial nerves as well as nerves in the extremities were involved

Antitoxin dose was 10 000 100 000 units that most often used was 40 000 units Size of dose depended on location of lesion whether one or more anatomic areas were involved and duration of disease Patient s weight was little considered in determining amount entire dose was given at one time In the later years of the period most patients received penicillin

(2) C 1 f Med 75 90 295 Octobe 1951

intramuscularly for one week or more without apparent effect on the course or incidence of complications However there was earlier disappearance of Corynebacterium diphtheriae from the respiratory tract in those patients receiving penicillin Tracheotomy for relief of respiratory obstruction was done for 22 patients 10 died

Relative increase in incidence in adults especially in those over 40 is probably due to protection of younger persons in the widespread immunization programs Diphtheria antitoxin is the single important agent in treatment of this disease and because of the need for immediate neutralization of circulating toxin the intravenous route appears to be the one of choice in most instances Exact dosage requirements cannot be stated since they vary between 20 000 100 000 units depending on site extent and duration of infection Underdosage and repeated small doses are to be condemned Serious serum reactions are rare although serum sickness is an annoying problem Administration of penicillin in no way modifies the antitoxin requirement and contributes little to successful outcome

Antibiotic Treatment of Pertussis Comparison of Penicillin, Aureomycin, Chloramphenicol and Terramycin in 150 cases was made by Lloyd N Hazen George Gee Jackson Chang Shih man Edwin H Place and Maxwell Finland[3] (Harvard Med School) The patients were studied clinically bacteriologically and serologically They were divided into two groups age 1 being used as the dividing point the therapeutic agent to be used in each patient was determined by rotation Each agent 60 mg kg body weight daily was given orally over 10 days in four doses Age distribution did not differ significantly among the therapeutic groups Most patients had had coryza with some cough for one to two weeks before hospitalization however in most paroxysmal cough was first noted only one or two days before hospitalization Disease was considered severe in 25% moderate in 43% and mild in 32% Chest x rays showed abnormalities in only six patients they were distributed quite evenly among the four antibiotic group

In patients treated with aureomycin terramycin or chloramphenicol Hemophilus pertussis disappeared fairly prompt

(3) J Pediat 39 1 15 July 1951

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A ALYSIS OF CLI ICAL EFFECTS OF A TIBIOT C THERAPY

	I N N	AUREO-M CIN	CHLO AM PHEN OL	TE A MY IN
Patients under age 1	18	1	13	7
Paroxysmal cough in hospital				
14 days or less	5	5	8	2
15 21 days	4	6	3	4
2 28 days	5	1	0	1
29 days or longer	4	0	2	0
Av no of days	21 8	15 6	13 8	14 1
No with fever after start of treatment	8	0	2	3
Av no days 100 F or higher	3		2	2
Av no of ho pital days	28	15 9	17 2	18 4
No with complications		0	2†	0
Clinical estimat of benef t				
Good	1	12	10	4
Equivocal	3	0	1	1
None	14	0	2	2
Patients over age 1	31	21	24	24
Paroxysmal cough in ho pital				
14 days or less	9	6	13	11
15 21 days	14	12	8	10
22 28 days	6	2	2	3
days or longer	2	1	1	0
Av no of days	18 0	17 4	13 5	14 5
No with fever after start of treatment	5	2	1	4
Av no days 100 F or higher	$1\frac{1}{2}$	3	1	3
Av no of hospital days	19.2	18 7	16 3	16 8
No with complications	1‡	3§	0	3¶
Clinical es imate of benefit				
Good	3	10	16	19
Equivocal	4	8	5	5
None	24	3	3	0

B onch pneumon a h p tal t n pat ent d f weeks fte tr t m t h

†B on hop m a bef r t tm nt l cal a d b t olog c r l pse one

‡P o h pn m h p tal z t

§Br h p e m h p taliz on ne l l nd bact of g el pse w th t hop m a ne taphylococc let f d n g t tm t ne

¶B hop mo e h p tal za ion n one st phylococ sca let fever d g t e tme t

intramuscularly for one week or more without apparent effect on the course or incidence of complications However there was earlier disappearance of Corynebacterium diphtheriae from the respiratory tract in those patients receiving penicillin Tracheotomy for relief of respiratory obstruction was done for 22 patients 10 died

Relative increase in incidence in adults especially in those over 40 is probably due to protection of younger persons in the widespread immunization programs Diphtheria antitoxin is the single important agent in treatment of this disease and because of the need for immediate neutralization of circulating toxin the intravenous route appears to be the one of choice in most instances Exact dosage requirements cannot be stated since they vary between 20 000-100 000 units depending on site extent and duration of infection Underdosage and repeated small doses are to be condemned Serious serum reactions are rare although serum sickness is an annoying problem Administration of penicillin in no way modifies the antitoxin requirement and contributes little to successful outcome

Antibiotic Treatment of Pertussis Comparison of Penicillin, Aureomycin, Chloramphenicol and Terramycin in 150 cases was made by Lloyd N Hazen George Gee Jackson Chang Shih man Edwin H Place and Maxwell Finland[3] *(Harvard Med School)* The patients were studied clinically bacteriologically and serologically They were divided into two groups age 1 being used as the dividing point the therapeutic agent to be used in each patient was determined by rotation Each agent 60 mg /kg body weight daily was given orally over 10 days in four doses Age distribution did not differ significantly among the therapeutic groups Most patients had had coryza with some cough for one to two weeks before hospitalization however in most paroxysmal cough was first noted only one or two days before hospitalization Disease was considered severe in 25% moderate in 43% and mild in 32% Chest x rays showed abnormalities in only six patients they were distributed quite evenly among the four antibiotic groups

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ANALYSIS OF CLINICAL EFFECTS OF ANTIBIOTIC THERAPY

	P	AU O-M	CHLO M ICO	T MYCIN
Patients under age 1	18	1?	13	7
Paroxysmal cough in hospital				
14 days or less	5	5	8	2
15 ?1 days	4	6	3	4
? 28 days	5	1	0	1
29 days or longer	4	0	2	0
Av no of days	?1 8	15 6*	13 8	14 1
No with fever after start of treatment	8	0	2	3
Av no days 100 F or higher	3		2	2
Av no of hospital days	22 8	15 9	17.2	18 4
No with complications	2*	0	2†	0
Clinical estimate of benefit				
Good	1	12	10	4
Equivocal	3	0	1	1
None	14	0	2	2
Patients over age 1	31	21	24	24
Paroxysmal cough in hospital				
14 days or less	9	6	13	11
15 21 days	14	1?	8	10
2? 28 days	6	2	2	3
29 days or longer	?	1	1	0
Av no of days	18 0	17 4	13 5	14 5
No with fever after start of treatment	5	2	1	4
Av no days 100 F or higher	1½	3½	1	3
Av no of hospital days	19.2	18 7	16 3	16.8
No with complications	1‡	3§	0	3¶
Clinical estimate of benefit				
Good	3	10	16	19
Equivocal	4	8	5	5
None	24	3	3	0

* [illegible]

† [illegible]

‡ [illegible]

§ [illegible]

¶ [illegible]

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Treatment of Pertussis with Aureomycin, Chloramphenicol and Terramycin. Although there has been almost universal agreement in literature that these drugs modify the clinical course of whooping cough Louis Weinstein Raymond Seltser and Charles T Marrow III[4] (Boston) report failure of the agents to influence the clinical course and point out occurrence of secondary bacterial and mycotic infections during treatment Of 80 patients treated 19 received aureomycin 25 terramycin and 36 chloramphenicol None of the three drugs significantly shortened period of whooping Neither aureomycin nor chloramphenicol promptly eradicated Hemophilus pertussis from the respiratory tract in all cases and in some instances the organism was still present even after treatment ended Terramycin appeared to be the most active in eliminating the infecting agent from the nasopharynx There was high incidence of recovery of certain potentially pathogenic organisms not detected in cultures taken before institution of therapy but noted during treatment Yeasts and monilia Proteus vulgaris and members of the coli aerogenes group appeared in detectable quantities in many patients and there was high incidence of isolations of Diplococcus pneumoniae from children given chloramphenicol Some complications due to secondary bacterial invasion were observed in the patients Of those receiving aureomycin superinfections were noted in six acute suppurative otitis media from which P vulgaris was isolated in pure culture was found in four patients and bronchopneumonia in two In one patient pharyngeal cultures revealed Escherichia coli Aerobacter aerogenes and Pseudomonas pyocyanea streptomycin parenterally resulted in rapid cure In the other Klebsiella pneumoniae was the predominant organism and treatment with sulfadiazine and streptomycin was effective Total incidence of complications was 31.2% Bronchopneumonia occurred in five patients receiving chloramphenicol The causative bacteria in three were the beta hemolytic streptococcus E coli and D pneumoniae (type VIII) in the other two no definite etiologic agent was identified Most disturbing was the appearance of potentially pathogenic organisms in the respiratory tract during therapy

(4) J Pediat 39 549 559 November 1951

In the final analysis reduction of the mortality rate to as near zero as possible in young children with pertussis is the ultimate objective However this was not accomplished in a greater degree in patients given specific therapy in the group receiving chemotherapy death due to encephalopathy and ob struction of the entire bronchial tree by thick mucus occurred in a child 3 months In over five years at the Haynes Me morial Hospital of 425 patients none of whom received any antibiotic unless a second bacterial infection supervened two children (0 44%) died Both were under 6 months occlusion of the bronchial tree caused death in one and massive cerebral hemorrhage in the other As chemotherapy may lead to super infections with organisms such as P vulgaris attempts at prophylaxis may lead to a more difficult situation than if the patient were not treated It is evident that bacteria such as Pneumococcus Streptococcus and H influenzae are highly sus ceptible to chemotherapy Treatment of choice for pertussis is good nursing maintenance of adequate nutrition hydra tion and electrolyte balance and recognition and early inten sive treatment of complications

[In the preceding two articles we find two comparable clinical studies by competent worker in the same city but with very different con clusions As a general rule when there is disagreement as to the worth of a treatment the eventual verdict is that the treatment is not very effec tive —Ed]

Epidemic Diarrhea in a School for Boys in October 1947 was characterized by nausea vomiting and diarrhea Of 193 boys 141 were affected during 10 days There were 61 in firmary admissions and 80 ambulatory cases In abruptness of onset attack rate and progression throughout the school community the disease resembled the pandemic of influenza in 1917 in the same school Nausea vomiting and diarrhea lasted less than 24 hours with no hospitalizations longer than 2 days Onset was often at night when sudden explosive vom iting awakened the boys Diarrhea was copious watery and free from mucus and blood Stools commonly numbered two to six within 12 hours and were free from common pathogens as was the vomitus Although most patients were afebrile approximately 25% had temperatures between 99 and 101 F White blood cells in five boys ranged from 6 200 to 9 600/cu mm

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vestigators (1935-40) and later of Reimann and others in the United States have led Theodore H Ingalls and Sidney A Britten[5] (Harvard Univ) to conclude that such diarrhea epidemics are disseminated by personal contact This is supported by illnesses among employees faculty and their families The hospital cleaning woman went home at 11 a m October 17 vomited and had diarrhea at 6 10 p m Her adolescent daughter who had not visited the school awoke ill at 2 a m October 19 The interval was approximately 32 hours Similarly the wife and son of an instructor became ill 74 and 86 hours after him A girl 10 visiting the home of another instructor became ill 70 hours after her host s illness and 86 hours after her arrival A student s mother became ill 3½ days after her son returned home and another son not at the school became ill 82 hours after his mother

Early recognition of the syndrome of nausea vomiting and diarrhea and the epidemiologic characteristics obviates the urgent sanitary measures required for food poisoning

Herpangina Clinical Studies of Specific Infectious Disease In recent summers a disease characterized by fever with vesicular or ulcerated throat lesions and chiefly affecting children has been prevalent in and around Washington D C In July and August 1950 it assumed epidemic proportion It has been recognized as a highly contagious benign self limiting disease which although previously poorly classified has recurred each summer Previous writers have described this entity under the names of herpetic pharyngitis and aphthous pharyngitis but the name herpangina suggested by Zahorsky seems satisfactory

Robert H Parrott Sidney Ross Frederic G Burke and E Clarence Rice[6] (Children s Hosp Washington D C) diagnosed 22 such cases in the early summer of 1950 in children aged 6 months to 8 years There was no correlation between age and severity Eight of the patients were siblings Sex and race differences were not significant Characteristically onset was relatively sudden without a prodrome The initial symptom was a high fever lasting 24 96 hours usually accompanied by anorexia and dysphagia Sore throat was noted in 60% of the children over 2 Fewer had vomiting and abdominal

(5) J A M A 146 710 71 J 23 1951
(6) New E gl d J Med 245 2 5 280 A g 23 1951

pains headache and generalized muscle pains were rare Respiratory manifestations (cough rhinitis otitis media) and meningeal irritation were conspicuously absent Physical examination revealed only diffuse pharyngeal injection with 1 2 mm discrete grayish white papulovesicular lesions with surrounding erythema on the anterior tonsillar pillars or soft palate Less often the lesions were noted on the uvula or tonsils 2 14 such lesions/patient were observed In two or three days the vesicles would enlarge slightly rupture having a grayish yellow ulcer with a more intense surrounding erythema Clinical course was benign self limited and without complications Penicillin therapy did not alter it

Routine cultures of pharynx and stools were not unusual White blood count showed no pattern about 50% having more than 10 000 cells/cu mm

Coxsackie type viruses were isolated from the feces of 19 of the 22 patients (86%) and from 45% of throat swabs by a team from the National Institutes of Health Immunologic studies revealed neutralizing antibodies against homologous strains of virus in all convalescent serums with a rise in titer from acute to convalescent serums in 70% Acute herpetic gingivostomatitis is the main differential dia nosis but other oropharyngeal lesions that must be differentiated include thrush the various aphthae of allergic traumatic or unknown origin the enanthems of measles varicella scarlatina and diphtheria Seven other patients with ulcerative oropharyngeal ulcers did not yield viruses on feces examination Many ill defined cases with such lesions have been reported but are inconsistent with the diagnosis of herpangina both in clinical history and type and distribution of the lesions

[We now believe the Coxsackie group of viruses to be responsible for three clinical entities (1) aseptic meningitis resembling non paralytic poliomyelitis (2) epidemic pleurodynia or Bornholm disease (3) herpangina —Ed]

TYPHOID FEVER

Sternal Marrow Cultures in Typhoid Fever The use of sternal marrow puncture for detection of the organism of typhoid has been stressed by several workers Gerbasi who claimed credit for the first systematic study of typhoid in children by bone marrow examination later used the method suc

cessfully in adults He stated that sternal marrow cultures often remain positive throughout the illness even when other tests are negative The bacillus may or may not appear in the blood during the initial febrile period but is a constant finding in the bone marrow

L Hirsowitz and R Cassel[7] (Baragwanath Hosp Johannesburg) carried out this procedure on 28 Bantu patients seen during a recent typhoid epidemic Positive cultures were obtained in 18 cases In five marrow cultures were positive when simultaneous blood cultures were negative In no instance was a blood culture alone positive

The authors suggest that sternal marrow puncture be more extensively used in the diagnosis of typhoid and paratyphoid infections

[Marrow culture appears to have advantages over blood culture not only in typhoid fever but also in other systemic *Salmonella* infections and in brucellosis —Ed]

Studies on Chloramphenicol in Treatment of Typhoid Fever are reported by Pedro T Lantin *Elpidio* L Gamboa and Filomena Sadili[8] (Manila Philippines) Although the disease is practically unknown today in most progressive countries it is still endemic in the Philippines

Fifty five patients were selected on the basis of approximately equal degree of severity of the disease and almost identical average duration of illness 24 were males Most were under 35 Clinical diagnosis was confirmed by blood cultures positive for Salmonella typhosa Chloramphenicol was administered to 31 patients 24 controls were treated symptomatically with the usual supportive measures The drug was given orally in initial doses of 1 25 Gm based on approximate body weight which were followed later by doses of 0 25 Gm repeated every two three or four hours during the febrile period On subsidence of temperature dosage was gradually reduced by lengthening the time intervals between doses over a week

In the chloramphenicol treated patients average number of days of fever from beginning of therapy was 4 48 during this period an average of 12 07 Gm chloramphenicol was given In the controls average duration of fever was 36 75 days counted from the day of onset of the disease as com

(7) Brit M J 1 86 863 Apr 1 1951
(8) Am J M Sc 2 15 295 September 1951

pared to 16 91 days in the treated patients There is therefore a difference of 19.84 days in favor of chloramphenicol ther apy Of the 31 patients treated with chloramphenicol 8 (25 81%) died Twelve controls died a mortality rate of 50% If it is thought that these rates were unduly high it must be remembered that all patients were selected on the basis of severity of disease

After chloramphenicol therapy had been stopped and fever had subsided repeated cultures were made in 18 cases (108 from blood 108 from feces and 86 from urine) All were negative for S typhosa In the treated patients the two prin cipal complications noted were one instance of intestinal hemorrhage and one of perforation of the vermiform ap pendix The most important complication in the control group was massive intestinal hemorrhage It occurred in eight pa tients six of whom died Of 23 patients who were treated and recovered 7 relapsed 5 with positive blood cultures dur ing the relapse Of 12 controls who recovered 5 relapsed

The outstanding effect of chloramphenicol was striking reduction in the course of fever

[There is no question of the value of chloromycetin® in typhoid fever but the disease is till a serious one —Ed]

BRUCELLOSIS

What Is Chronic Brucellosis? There is a wide divergence of opinion concerning the concept of chronic brucellosis many maintaining that it is prevalent and many denying that it is a recognizable entity Wesley W Spink[9] (Univ of Minnesota) discusses the criteria necessary for diagnosis of active dis ease and stresses that laboratory technics are indispensable since the clinical features are not specific Since dermal hyper sensitivity to brucella antigens may persist for many years after the initial infection the skin test is of no value in indi cating active disease This holds true no matter how the anti gen is prepared However with a reliable antigen under op timal testing conditions one can rely strongly on results of agglutination tests These tests are the most dependable aids other than actual isolation of the organism

(9) A I t M d 35 358 374 A gu t 1951

Misconceptions that agglutinins for brucella are frequently absent and hemocultures are rarely positive in chronic brucellosis or that brucella may be cultured in the absence of agglutinins are apparently widespread Results of several thousand examinations at the University of Minnesota Hospitals showed that it is extremely rare to recover organisms from the blood in the absence of agglutinin Over 90% of patients with bacteremia had a titer of 1 320 or higher

It is unusual to obtain brucella from the blood of patients with active disease of over a year s duration unless localizing complications are present Occasionally the organisms may be cultured from aspirated sternal bone marrow urine draining sinuses and biopsy specimens of lymph nodes of such patients Brucella organisms have been isolated from about half the patients who were considered to have active brucellosis

Because of the many patients with ill defined symptoms who are suspected of having active chronic brucellosis and because of the unreliability of various diagnostic and therapeutic procedures an effort was made to gain some understanding of the disease by studying 65 patients who had had acute brucellosis Follow up periods ranged from 1 to 13 years (average 4½) Of these patients 53 were males This sex preponderance is the rule although many uncritical reports on chronic brucellosis deal largely with females Thirty patients (46%) had chronic brucellosis their ill health persisting for more than one year Of these 13 showed no objective evidence of active disease but complained of ill health with almost monotonous regularity vague aches and pains easy fatigability nervousness and mental depression The other 17 patients considered to have chronic brucellosis had either (1) a relapsing febrile illness confirmed by laboratory study or (2) evidence of localization of the disease in various organs or tissues again confirmed by laboratory procedures

There appear to be three possible explanations for the complaints of the unconfirmed group (1) continued active infection which has not as yet been substantiated (2) an independent neurotic basis for the symptomatology and (3) possible organic damage to the cerebral cortex as suggested by some on the basis of psychometric examination of patients with known chronic brucellosis Difficult as the diagnosis of chronic brucellosis is Spink doubts the validity of such a

diagnosis based on (1) subjective complaints only (2) a positive intradermal test with brucella antigen and (3) absent or low titer of brucella agglutinins

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PYOCYANEUS INFECTIONS

Infections with Pseudomonas Aeruginosa Treated with Polymyxin B This organism is not normally a pathogen since it has no invasive powers and is ordinarily dealt with by the normal defenses of the body Should these defenses not be developed as in infants or break down as in debilitated persons or should the bacillus be introduced passively into areas devoid of adequate natural defense mechanisms an infection can develop Pseudomonas aeruginosa synthesizes its proteins from simple compounds making interference with essential enzyme systems difficult this accounts in part for resistance of this organism to most antimicrobial agents Pseudomonas species also adapt well to unfavorable environments consequently they readily acquire resistance to antibiotics The antimicrobial agent most active against this organism is polymyxin the least toxic polymyxin B

Ernest Jawetz[1] (Univ of California) reports results of treatment with polymyxin B sulfate in 35 cases of pseudomonas infections (table) Because of the question of nephrotoxicity of the polymyxins renal function of the patients receiving polymyxin B parenterally was checked carefully Studies included in addition to routine urinalyses determination of urinary protein excretion blood nonprotein nitrogen and serum creatinine levels creatinine clearance phenolsulfonphthalein excretion and Addis counts at frequent intervals Among 28 patients treated intramuscularly there was a slight transient increase in proteinuria in 7 and a significant increase in Addis count in 3 These changes regressed a few days after discontinuance of therapy No other abnormalities were encountered on the contrary there were four instances in which an originally elevated serum creatinine or blood nonprotein nitrogen level returned to normal during therapy

Other side reactions consisted of irritation at the injection site and neurotoxic symptoms i e circumoral and peripheral

(1) A M A A b I t M d 89 90 98 J y 1952

Results of Polymyxin B Treatment in Patients with Infections Due to Ps Aeruginosa

Type of Infection	Patients	Route and Dose	Results
Pyelonephritis acute	4	1 5 ?8 mg /kg /day I M for 6 8 days	Permanent cure in all patients
Pyelonephritis chronic	8	1 5 ?5 mg /kg /day I M for 6 11 days	Temporary suppression of organisms with improvement later relapse in all
Meningitis	2	5 mg intrathecally q i d then every 2 days for 2 3 wk	Permanent cure without sequelae in 1 cerebrospinal fluid sterilized but late hydrocephalus developed in 1 treatment begun too late
Arthritis purulent	1	10 ml daily of sol of 1 mg /ml injected into joint for 5 days	Eradication of organisms in 6 days
Conjunctivitis	2	Solution of 1 mg /ml instilled q i d for 5 days	Discharge stopped organisms eradicated
Otitis media chronic	5	Solution of 1 mg /ml instilled q i d for 6 days	Discharge stopped organisms eradicated
Sinus tract infected	3	Solution of 1 mg /ml instilled t i d for 5 10 days	Organisms eradicated and sinus healing in 2 superinfection with Proteus vulgaris in 3d
Sinusitis maxillary chronic	1	Irrigation with sol of 0 5 mg /ml daily for 7 days	Discharge diminished organisms eradicated
Wound infection	9	Sol of 1 mg /ml topically (continuous wet dressings) and instilled into wound for 4 10 days	Discharge stopped organisms eradicated and prompt healing of wound in 8 1 not affected

paresthesias moderate dizziness and a feeling of weakness without objective signs All neurotoxic symptoms disappeared within 24-48 hours after injections were discontinued

Resistance to polymyxin B does not develop readily In the present series escape of bacteria from the suppressive action of the drug was observed *only once* This drug exerts its most beneficial action in processes localized on surfaces or within closed systems Topical administration even for prolonged periods is quite safe since so little is absorbed from mucous membranes or wounds

With apparent increasing frequency of Ps aeruginosa infections polymyxin B should fill a real need in clinical practice

[As in the case of bacitracin (this YEAR BOOK p 20) renal toxicity of this antibiotic seems to have been somewhat overemphasized Polymyxin may have unique value in selected instances especially pseudomonas (pyocyaneus) infections —Ed]

Pseudomonas Aeruginosa Infection as Complication of Therapy in Pancreatic Fibrosis (Mucoviscidosis) was observed in four patients by Sterling D Garrard Julius B Richmond and Marvin M Hirsch (Univ of Illinois) Although Staphylococcus aureus infections of the respiratory tract were formerly common in patients with this disease the newer antibiotics have decreased thi incidence Nevertheless infectious complications *persist* with Ps aeruginosa predominating This organism is initially highly resistant or readily acquires resistance to all available antibacterial therapy and hence persists in an infected area after other bacteria are eliminated It was formerly considered a relatively harmless contaminant of bacterial cultures because of its lack of invasiveness but review of the clinical literature contradicts this impression Infants children and debilitated adults are most often infected In the four patients studied superinfection with this organism occurred in the tracheobronchial tree and was eventually associated with the terminal illness in at least three These children had received antibacterial therapy over a period of one to five years Continuous prophylactic antibiotic therapy thus appears open to question Regardless of the pattern of resistance prolonged therapy with one agent will lead to emergence of resistant strains especially of Ps aeruginosa and those bacteria with a high

( ) P d t 8 48 488 Octobe 1951

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Type of Infection	Patients	Route and Dose	Results
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(2) P d t 8 48 438 O tob 1953

degree of initial resistance Logically, therapy for pancreatic fibrosis should be intermittent to prevent superinfection with resistant bacteria

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TUBERCULOSIS LEPROSY

Acute Tuberculous Septicemia with Leukopenia. No case reported has been recognized during life but in view of the possibility of using chemotherapy early diagnosis is desirable Keith Ball Horace Joules and Walter Pagel[3] report three cases with autopsy data All were seen on the same medical unit within four years and in each an obscure clinical picture with pyrexia severe leukopenia and rapid downhill course was present

Man 54 had been well until three weeks before admission when chills developed followed by sweating He was extremely ill and had herpes labialis furred tongue chest petechiae and impaired resonance with diminished breath sounds at the base of the right lung No abnormal signs were present in other systems White blood cells numbered 925/cu mm (neutrophils 72% lymphocyte 21% monocytes 5% eosinophil 2%) White cell count rose later to 1 100 and 1 450 with 86% neutrophils on each occasion Hemoglobin level was 69% red cell count 4 400 000 and color index 1 0 Sputum gave a growth of Staphylococcus aureus and pneumococci No tubercle bacilli were seen X ray films of the chest showed some consolidation at both bases Temperature was irregular up to 101 1 Diagnosis was pneumonia with leukopenia and penicillin and liver extract were given He steadily became worse and died eight days after admission

These 3 cases bring the number of fully recorded ones to 11 Eight were in men and ages varied from 22 to 56 (average 44) The acute illness which was invariably fatal lasted 3 12 weeks Rigors anorexia and malaise were the most frequent symptoms and in all cases there was high fever of no constant type The spleen was enlarged in six cases and the liver in three Jaundice was present twice In two cases there was a history of widespread skin eruption before admission and in one case a papular eruption was found on the legs Ulceration of the fauces was noted only twice during life just before death but it was found in two other cases at autopsy In eight cases the total leukocyte count fell below 1 000/cu mm but in only three of nine cases in which dif

(3) Brit M J 2 869 873 Oct 13 1951

ferential counts were made did the neutrophil percentage fall below 40 The hemoglobin level was 60% or below in 6 of 10 cases in which it was recorded and the color index was usually high The platelets were markedly diminished in three cases Sternal puncture revealed depression of the granulocytes in two aplasia of the bone marrow in a third case and a normal marrow in a fourth Thus it appears that depression of one or all of the blood forming elements usually occurs Although severe leukopenia is a striking feature it is probably a complication rather than an essential feature of the disease The authors believe it is caused by the action of the tubercle bacilli on the bone marrow

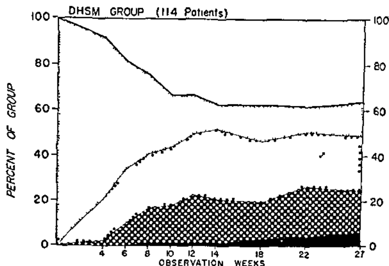
Since the disease is rapidly fatal early diagnosis would be necessary for chemotherapy to have a chance of success The clinical picture often suggests typhoid fever or miliary tuberculosis but diagnosis depends on awareness of the entity and finding the bacilli Bone marrow punctures may be the best method of obtaining samples for culture Streptomycin might effect a cure if given before irreversible changes had occurred A trial of the drug would be fully justifiable in what is an otherwise hopeless condition

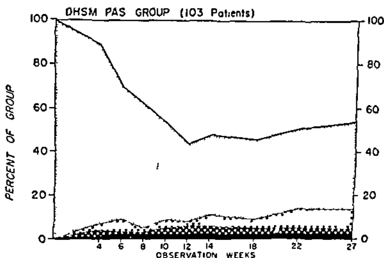
[This dramatic entity must be comparatively rare but since it might be expected to respond favorably to streptomycin clinicians should be aware of the syndrome —Ed]

Effect of PAS on Emergence of Tubercle Bacilli Resistant to Streptomycin Effectiveness of streptomycin in treatment of tuberculosis has one serious limitation namely the ability of the tubercle bacillus to adapt itself to presence of the antibiotic Studies made by U S Public Health Service[3] showed that bacterial populations readily developed mutants in the presence of one drug or another but no doubly resistant mutants could grow out in the presence of two independently acting drugs In this way a second drug might be expected to delay the emergence of streptomycin resistant organisms

A report is presented on the effect of para aminosalicylic acid (PAS) on the emergence of streptomycin resistant tubercle bacilli in patients with pulmonary tuberculosis Results of in vitro streptomycin sensitivity tests on cultures of tubercle bacilli isolated from sputum specimens from 103 patients given dihydrostreptomycin and PAS are compared with results in 114 patients given dihydrostreptomycin alone (Fig

(3) P b H lth R p 66 863 87 July 6 1951





Negative — Positive — Dead





Se tive

R s ont to 10 MCG

R on t 100 MCG



F g —P ntage d t but on f d hyd st pt my l d hyd t p myc PAS g o p b bact l g d t pt my t t t tu t 10 po t f t m (C t y f U S P bl H lth S c P b H lth R p 66 863 872 J ly 6 1951)

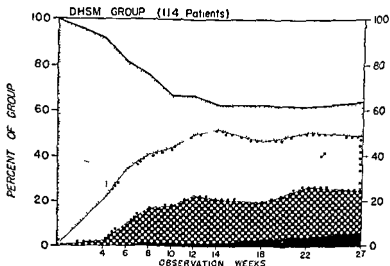
2) Data were obtained in a co operative study initiated by the National Institutes of Health

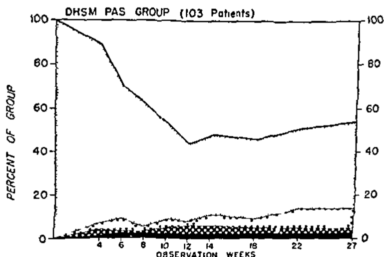
At the 14th week the first observation point after the end of drug therapy tubercle bacilli were not cultured from the sputum of 37% of the dihydrostreptomycin group and from 52% of the dihydrostreptomycin PAS group Streptomycin resistant organisms were found in cultures from 51% of the dihydrostreptomycin patients and only 9% of the dihydro streptomycin PAS patients The action of PAS in suppressing the emergence of streptomycin resistant bacilli is apparently not confined to any particular type of case

Disturbances of Ionic Equilibrium of Intracellular and Extracellular Electrolytes in Patients with Tuberculous Meningitis Reductions of serum chloride and sodium values are consistently found in children with tuberculous meningitis Harold E Harrison Laurence Finberg and Evelyn Fleishman[4] (Baltimore) made serial determinations of plasma and red blood cell electrolytes on 16 children treated with streptomycin to obtain information on the nature of these changes In addition analyses were made of skeletal muscle biopsies from four children at times when serum chloride and sodium concentrations were reduced

Determinations revealed a reduction of plasma sodium and chloride with relatively normal values for plasma bicarbonate potassium urea nitrogen and total protein Serum calcium was in the lower range of normal and serum phosphorus was reduced Representative data are shown in the table Determinations of the Evans blue thiocyanate and antipyrine spaces (indexes of plasma volume extracellular fluid volume and total body water) in several patients with low sodium concentrations showed no evidences of reduction i e losses of extracellular electrolytes were not accompanied by losses of extracellular fluid During clinical remission serum sodium and chloride values returned to normal without changes in potassium or bicarbonate values When the low serum sodium concentrations are considered the data are in accord with reports of excessive urinary losses of sodium in three children with tuberculous meningitis and with the conclusions of others that renal wastage of sodium and chloride

(4) J Cl I 1 31 300 308 M h 195





Ne ative



Pos tive





R s ont
100 MCG

Dead



F g —P r ntage d t b t on f d hyd t pt m l d hyd t pto- myc PAS g p by b ct log d st p my t t t t 10 p t of t me (Court y f L S P bl He lth S r I b H lth R p 66 863 872 J ly 6 1951)

and general measures for improving the patient s resistance caring for complications and correcting already existing de formities have significantly altered the outlook for even the most severely diseased patient

In its untreated natural course leprosy ranges in gravity from the benign spontaneously healing condition to the severe disease with its unfavorable progress through periods of spontaneous remission and exacerbation Such measures as improvement in general health elimination of intercurrent in fections alleviation of physical and mental strain and adequate diet are necessary for favorable effect on the outcome because whatever the form of special treatment it is likely to be pro longed and strenuous

A common point of agreement is that chaulmoogra oil is effective in milder type of the disease and in more malig nant types if the patients can tolerate adequate dosage by intramuscular and intracutaneous routes many lack the neces sary tolerance In places where both the oil and sulfones have been used it has been found that treatment with sulfones can be prolonged over greater periods much more easily than is possible with chaulmoogra oil Sulfone drugs are regarded as the agents of choice most widely used are glucosulfone sodium (promin®) sulfoxone sodium (diasone) and sulphe trone Certain definite shortcomings have appeared but bene ficial therapeutic effects far outnumber the deficiencies

Clinical improvement begins in the early weeks of treat ment and almost complete clearing of skin and mucous mem brane lesions is seen except for residuals in one to three years After improvement in the skin and mucous membranes the number of leprosy bacilli in these tissues is reduced This reduction however is exceedingly slow compared to the speed of clinical improvement The occurrence of erythema nodosum a good prognostic sign commonly increases during treatment Sulfones by their suppressive action appear to counteract the formation of new leprous lesions and thereby allow the body defenses to inactivate the disease Surgical correction of orthopedic and facial deformities and physio therapeutic measures for prevention of deformities are perma nently successful Sulfone drugs may be given over long periods without any serious toxic reactions Several patients at Carville have taken glucosulfone sodium for nine and sul

may occur in pulmonary tuberculosis without evidence of adrenal insufficiency

Muscle sodium was higher and muscle potassium considerably lower in the children with tuberculous meningitis than in controls The increased ratio of sodium to chloride in the muscle suggests an accumulation of sodium in muscle fiber

SERUM ELECTROLYTES* OF CHILDREN SHOWING MARKED REDUCTION OF SODIUM AND CHLORIDE CONCENTRATIONS DURING TUBERCULOUS MENINGITIS

PATIENT	NA	CL	CO	K	CA	P	UREA N	PROTEIN†
1	122	848	22.6	49	88	3.6	116	68
2	119	816	243	—	91	42	156	7.3
3	124	888	240	40	—	—	142	—
4	124	896	27 4	53	—	—	171	—

*Na Cl CO and K in m Eq /L and Ca P and urea N in mg /100
†Protein in Gm /100 cc

whereas a reduction of the ratio of potassium to nitrogen indicates depletion of cell potassium

These studies reveal a characteristic pattern of disturbance of electrolyte equilibrium in patients with tuberculous meningitis In extracellular fluid sodium and chloride concentrations are reduced without consistent change in potassium concentration in red blood cell water there is increased concentration of sodium and no change in potassium so that the concentration of total univalent cations is increased in muscle water there is an increase of sodium with a concomitant decrease of potassium In severe tuberculous infections there is a disturbance of the mechanisms governing ionic equilibrium between cells and extracellular fluid Renal loss of sodium and chloride with consequent reduction of their concentrations in extracellular fluid may be one aspect of this more general abnormality

[Increasing clinical use of electrolyte determinations has revealed that not only tuberculous meningitis but also pulmonary tuberculosis may give rise to changes of this type Hence the finding of low serum sodium concentration in a patient with tuberculosis does not prove that he has Addison s disease —Ed]

Treatment of Leprosy is discussed by Paul T Erickson[6] (Lexington Ky) The introduction of the sulfone drugs in 1941 was the most important single therapeutic advance These with the help of other new chemotherapeutic agents

(6) A   New Y k Acad S   54 115 1 5 A t 3 1951

procedures Before the advent of antibiotics many agents were used for therapy of leptospirosis including arsenical and bismuth compounds and immune serum but none stood the test of time Sulfonamides were devoid of therapeutic value and recently numerous investigators have described the bene ficial effects of penicillin in human cases In contrast other investigators were not at all impressed with penicillin in any stage of this disease

The authors gave chloramphenicol to 18 patients aureo mycin to 13 penicillin to 5 terramycin to 8 streptomycin to 12 combined aureomycin and streptomycin to 9 and cortisone and aureomycin to 2 who were critically ill Studies revealed the variability in severity of leptospirosis of man and the difficulties encountered in attempting to evaluate chemo therapeutic agents None of the antibiotics used was par ticularly effective in this disease and it is doubtful whether any are worthy of future use in leptospirosis Further search for satisfactory therapeutic agents against leptospirae is in dicated Methods should also be found for supporting severely ill patients during toxic damage to parenchymatous organs and repair of these lesions

[Here is a reliable report based on observation of an adequate num ber of cases Many individual case reports have claimed therapeutic efficacy of this or that ant biotic Such reports must be viewed skeptically because leptospiral infections are so variable —Ed]

Leptospirosis in England and Wales Leptospires are primarily parasites of rodents though some have become adapted to pigs cattle and dogs Often they are so well adapted to their normal host that they establish large colonies in the renal tubules without producing deleterious effects on *the animal host Intermittently some of the leptospires pass* out in the urine If they reach water which provides suitable conditions they can survive for weeks They enter new hosts through broken skin or mucous surfaces and the cycle con tinues If the new host is man or a susceptible animal disease results It has never presented itself in a dramatic epidemic in man The most widely distributed form is leptospirosis icterohaemorrhagica (Weil s disease) due to Leptospira ictero haemorrhagiae

J C Broom[8] (London) had access to the records of almost all the reported cases (465) in England and Wales

(8) B t M J 2 689 697 S pt 22 1951

foxone sodium for seven years continuously without any serious toxic effects A depression of erythrocytes is the most frequent toxic manifestation and usually occurs in the first few weeks of treatment often returning spontaneously to the original level Leukopenia allergic dermatitis and rhinitis mild and ephemeral headaches and nausea are other toxic effects that have been recounted

The most serious deficiency of sulfone treatment is the great slowness with which it eliminates the leprosy organism from its normal habitat in the skin and nerves Leprosy bacilli may be found in previously involved skin areas years after clinical healing Nerve trunks of patients in whom the disease had long been inactive have been found at autopsy to harbor leprosy bacilli At Carville of 460 patients treated with sulfones for one to nine years the disease has been arrested in 109 arrest is assumed after one continuous year of negativity of the skin and mucous membranes for Mycobacterium lepra and other evidences of clinical activity

Regular rest periods from sulfone therapy are recommended as a safety measure Fairly high drug concentrations have been found in the blood urine skin and liver two to four weeks after discontinuance of drugs in patients who have taken them over long periods Rest periods allow release of the drugs from tissues before critical levels are reached After apparent arrest maintenance doses of sulfones should be given indefinitely to avoid relapses

[The treatment of leprosy is of course highly specialized practice nevertheless it is worth while for all of us to peruse a progress report from time to time —Ed]

SPIROCHETAL INFECTIONS

Evaluation of Antibiotic Therapy in Human Leptospirosis Studies on the therapeutic effects of five antibiotics on 67 patients with leptospirosis were made by H E Hall J A Hightower Diaz Rivera R J Byrne J E Smadel and T E Woodward[7] Diagnosis was confirmed by isolation of leptospirae from blood urine or cerebrospinal fluid by demonstration of development of specific antibodies or by both

(7) Ann I t M d 35 981 998 N embe 1951

reports are occasionally favorable but not infrequently the drug was first given at a relatively late stage of the illness when a favorable outcome was already established The critical point in the disease is about the 14th day for at about this time death usually occurs as a result of uremia following renal damage In this series 206 patients with Weil s disease received penicillin with 34 deaths This represents a crude mortality rate of 17% which is not much different from the over all rate of 15% Other antibiotics have not had a wide enough trial

Leptospiral Meningitis Although cases of Weil s disease have been recognized in various parts of the United States leptospirosis particularly the less spectacular clinical pat terns is probably more common than appreciated since the disease has been found in rats and dogs throughout the country In general leptospiral infection may be classified as icteric or anicteric The icteric form (Weil s disease) is the more severe and has a distinct clinical picture of sudden onset with fever chills muscle pains conjunctival effusion and after about five days as the fever subsides evidences of hepatitis and nephritis may appear In 90% there is also a pleocytosis in the spinal fluid The anicteric cases have various designations (cane fever swamp fever etc) and are generally mild grippelike illnesses lasting a few days Some have two febrile periods separated by a day or so of normal tempera ture Signs of meningitis are common and such cases can be mistaken for instances of benign aseptic meningitis

Paul B Beeson and Daniel D Hankey[9] (Emory Univ) studied all of 35 cases admitted to Grady Hospital over two years with the diagnosis of benign aseptic meningitis to detect leptospiral infection Cultures agglutination tests animal in oculations and direct darkfield examination of body fluids were done and six cases were detected (plus one from a nearby hospital) In addition serologic evidence was obtained in 17 of about 500 pairs of serums from other laboratories col lected often during epidemics of poliomyelitis mumps and encephalitis Because of this selection the authors believe that the true incidence of sporadic cases of leptospiral menin gitis is not well revealed

Leptospiral meningitis is a disease of younger persons

(9) A M A A h I t M d 89 575 583 Ap 1 195

from 1947 to 1950 The death rate was 15% and the incidence of jaundice 74% as compared with rates of 22 and 90% for 1940-46 These two findings are probably closely related as deaths in nonicteric cases are rare In this series 95% of the patients were male The high preponderance of males was due to the manner in which the infection is contracted (Table 1)

Canicola fever a *milder form of leptospirosis* caused by L canicola *is endemic in dogs hence it is a domestic rather than an occupational disease The infectivity of L canicola*

TABLE 1—OCCUPATIONAL INCIDENCE IN WEIL'S DISEASE (1947 50)

	%
Farm workers	31 0
Bathing and accidental immersion	19 0
Sewer workers	5 0
Coal miners	4 0
Handlers of food	4 0
Fish workers	3 5
Working in water	2 5
Miscellaneous	31 0

TABLE 2—SYMPTOMS IN 54 HUMAN CASES OF CANICOLA FEVER

	%		%
Headache	90	Albumin in urine	43
Meningitis	78	Casts in urine	14
Stiffness of neck	78	Rash	20
Injection of eyes	58	Jaundice	18
Muscle tenderness	58	Hemorrhages	16

is apparently low because only those persons cleaning up the dejecta of dogs have contracted the disease The clinical symptoms observed in 54 cases are shown in Table 2 Complete recovery is the rule

In leptospiral meningitis the cerebrospinal fluid glucose concentration is generally above 50 mg /100 ml The authors studied the serums in 642 cases of aseptic meningitis not due to virus infection by agglutination reactions to various leptospiral organisms In no instance was there any indication of infection with organisms other than L icterohaemorrhagiae or L canicola However 17 cases of the pure meningeal form of Weil's disease and 8 of canicola fever were discovered Muscle and liver biopsies may perhaps aid in early diagnosis

Therapy with penicillin has not been proved as efficacious when significant numbers of cases are considered Individual

tions headache generalized muscle pain arthralgia cramping abdominal pain and persistent fever Onset was insidious and associated with nausea and malaise No insect vector was incriminated Temperature was 104 F on admission Physical examination revealed pharyngitis and tenderness in the right upper abdominal quadrant White blood cell count was 14 800 with a normal differential count The icterus index was 8 and thymol turbidity 6 units Borrelia spirochetes were noted in the blood smear After the third injection of penicillin temperature fell to normal and recovery followed a 10 day course of therapy Spirochetes were no longer demonstrable after 24 hours

Congenital Syphilis in Massachusetts Nicholas J Fiumara (Massachusetts Dept of Pub Health) analyzed 59 cases in children born during 1946-50 to determine reasons for per

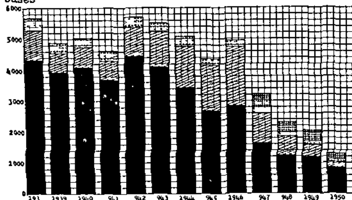


Fig 3—R po t d ca f yph l by tag M h ett (C rte y f F N J N w E gl d J M d 45 634 640 O t. 25 1951)

sistence of the condition despite availability of penicillin therapy and premarital and prenatal examination laws

Figure 3 indicates how few cases of syphilis are discovered and reported during the primary and secondary stages This leads to the question of how syphilis can be controlled when for every case of manifest syphilis reported five other patients are known to have been missed during the most infectious stages

( ) N w E gl d J M d 245 634 640 O t 25 1951

The age range was 10 55 in this series of 24 19 were under 30 Only 5 were female 21 were white Ten cases occurred in August none in December or January Onset was generally abrupt without a prodrome All patients had headache and fever In most cases fever was over 102 F at some time and lasted 5 days to 3 weeks usually only 8 12 days Conjunctival suffusion was present in four of seven patients observed and two of them had conjunctival hemorrhages also Nuchal rigidity occurred in most cases Routine blood and urine tests were normal Spinal fluid pleocytosis was noted in all usually at the first examination The counts were highest between 8 and 15 days but seldom over 300 a point of differentiation from lymphocytic choriomeningitis and mumps meningitis Early as many as 50% of the cells were neutrophils but after 12 days they seldom exceeded 30% The protein was usually slightly elevated and the glucose was always normal Leptospiral agglutination tests ranged in titers from 1 400 to 1 12 800 Of these 10 were against Leptospira icterohaemorrhagiae 12 against L canicola and 2 against L pomona Titers were demonstrable in about 8 10 days with a peak at the end of two to three weeks

It is concluded that leptospiral meningitis occurs in many parts of the country and is not more often recognized because (1) the causative organism is not demonstrable by conventional bacteriologic cultural methods and (2) the clinical picture closely resembles that evoked by neurotropic virus infection i e lymphocytic cellular exudate in the spinal fluid and normal dextrose content of the spinal fluid Preparation of a satisfactory antigen for use in routine clinical laboratories would doubtless lead to increased recognition of all forms of leptospiral infection

Antibiotics in Treatment of Relapsing Fever Although penicillin in conventional doses has been disappointing in the treatment of relapsing fever Ira B Harrison and Richard M Whittington[1] found that when used in high doses (aqueous penicillin 200 000 units every six hours) it was efficacious in six cases There was a prompt response in all and no relapses or Herxheimer reactions were observed In one case aureomycin gave equally *good results*

Youth 19 had a five day illness characterized by chilly sensa

(1) U S Armed F c M J 1859 186 December 1951

Both the ECG and EEG were normal Roentgen examination re vealed in the mid third of the left tibia an area of gross periosteal calcification which formed a fusiform shadow surrounding the shaft and extending about 3 in (8 cm) There was further periosteal calcification of a smaller amount extending down along the lower tibial shaft to the level of the ankle A triangular area of rarefaction was present in the lesion along its inner side and in or adjacent to the inner cortex On the right leg there was a similar lesion at the junction of the middle and distal third showing extensive periosteal calcification in a fusiform shape and mainly along the inner side of the shaft A third lesion of almost the same type was present in the fibula on the right side at the junction of its upper and middle third There was no evidence of overlying soft tissue mass in any of these areas A lesion involving the metacarpal of the left thumb resembled those in the legs it consisted of dense periosteal calcification sur rounding the entire shaft more striking on the outer side Roentgen diagnosis was syphilitic osteoperiostitis of the tibia and fibula bi laterally and of the left first metacarpal Biopsy confirmed this im pression

Aureomycin 3 0 Gm was given with milk daily (three 0 25 Gm capsules four times a day) Within 24 hours she complained of severe pain in both legs and fever was noted This was interpreted clinically as a Jarisch Herxheimer reaction The pain diminished with continued medication Total of 50 Gm was administered with out nausea or other gastrointestinal symptoms Six months after completion of therapy she stated that her feet and legs had not troubled her for four months Cerebrospinal fluid examination and roentgenologic studies of the legs and left thumb showed striking improvement There were reduction of the periosteal thickening general smoothing off of the periosteal shadow and filling in of the areas of rarefaction

[That aureomycin has therapeutic activity in syphili is now largely a matter of academ c interest It place as compared with penicillin will probably not be defined because of the dwindling reservoir of clinical material and the long term study necessary for conclusions —Ed]

MYCOTIC INFECTIONS

Histoplasmosis in Epidemic Form In an earlier report Benjamin Schwartz and Leon J Spitz[4] (Veterans Admin Brooklyn) described 26 cases of diffuse pneumonitis which occurred as an epidemic at an army camp in 1944 under the title An Unusual Pulmonary Disease On the basis of fol low up in one case they now believe the epidemic was due to Histoplasma capsulatum

(4) A M A A h I t Med 89 541 546 Ap 1 195

This study showed that congenital syphilis occurred because of the following factors (1) ignorance and carelessness of mothers in not seeking prenatal care (30%) (2) failure to return to the physician s office for treatment (20%) (3) inadequate treatment because of failure to return regularly for completion of scheduled treatment (17%) (4) infection of mother subsequent to initial negative blood reaction (12%) (5) relapse or more probably reinfection (5%) (6) treatment failure i e treatment was given late in pregnancy and completion of it coincided with onset of labor (3%) (7) failure on the physician s part to perform a blood test for syphilis (5%)

The following recommendations are made A blood test for syphilis should be performed on all new patients Women who have been adequately treated for syphilis and are seronegative should have blood tests at least once in the first and second trimesters of pregnancy and monthly during the last trimester At least two tests one performed early and the other late in pregnancy should be made on all women known to have been sexually promiscuous women with a history of any venereal disease and single divorced or separated pregnant women Women who have been adequately treated for syphilis but are still seropositive should be re treated with penicillin during each succeeding pregnancy Intensified educational efforts should be made to persuade mothers and potential mothers to seek early adequate prenatal care Patients with positive reactions to prenatal serologic tests who neglect to return for diagnostic study and treatment should be referred to the department of public health

[The author is properly concerned about methods of preventing every possible case of congenital syphilis to me however the interesting thing is his graph showing the spectacular decrease in all forms of syphilis since the introduction of penicillin treatment in 1943 —Ed]

Use of Aureomycin in Case of Osteoperiostitis of Syphilis Frank W Crowe and Sture A M Johnson[3] (Univ of Wisconsin) state that aureomycin has been used successfully in primary secondary and tertiary syphilis but that this is the first report of its use in osteoperiostitis

Woman 59 complained of pain and swelling of the legs and ankles Quantitative blood Wassermann reaction was 3 + Cerebrospinal fluid studies showed syphilis of the central nervous system

(3) A M A A h D rm t & Syph 64 757 760 D mbe 1951

form diagnosis is more difficult because the organism is not as readily isolated Reactions to skin and complement fixation tests often are negative in the acute phase and early convalescence adding to difficulty in establishing the diagnosis Chest x ray signs in the acute stage are not characteristic but in the presence of disseminated pneumonitis with or without enlargement of the hilar nodes histoplasmosis should be seriously considered

[It is satisfying that the etiology of this and several other reported outbreaks of acute disseminated pneumonitis including that known as cave pneumonia has definitely been established as histoplasmosis —Ed.]

Aureomycin in Treatment of Actinomycosis Leon V McVay Frances Guthrie and Douglas H Sprunt[5] (Univ of Tenn) add two cases of cervicofacial actinomycosis to one previously reported and one of actinomycotic hepatic abscess in which treatment with aureomycin was successful

Numerous therapeutic agents have been used but only after advent of the sulfonamides and penicillin was prognosis materially improved although despite their prolonged and combined use and appropriate surgery morbidity and mortality have remained significantly high This is especially true in the thoracic and abdominal forms of the disease Successful use of aureomycin in these patients is therefore important It is noteworthy that major surgery was not required Although post therapeutic observation periods in the four cases are relatively brief the uniformly excellent response is most encouraging In view of the rapid clinical response ease of administration and lack of significant toxic effects aureomycin seems the agent of choice The four patients observed at monthly intervals for 17 14 13 and 12 months have had no evidence of recurrence

Coincidence of Cryptococcosis and Disease of Reticuloendothelial and Lymphatic Systems Human infection by the pathogenic fungus Cryptococcus neoformans (known under some 68 names including Torula histolytica) is most commonly recognized when the central nervous system is involved Vincent P Collins Alfred Gellhorn and James R Trimble[6] (Columbia Univ Presbyterian Hosp) call attention to reticuloendothelial pathology usually manifested as lymphadenopathy which is a frequent accompaniment (51 of 243 col

(5) N w E gl d J Med 245 91 96 J ly 19 1951
(6) C 4 883 889 J ly 1951

Man 36 when hospitalized in 1944 was acutely ill complaining of chills fever sweats generalized aching headache and nonproductive cough He and 25 copatients with similar symptoms had been required to stay in an abandoned storm cellar during one evening Temperature was 102 F pulse rate 90 and respiratory rate 18 Although physical examination gave essentially normal results chest x rays revealed diffuse mottling throughout both lung fields with bilateral hilar node enlargement The acute phase lasted one week with temperature range of 102 104 F Thereafter the fever gradually subsided followed by recovery Serial chest x rays revealed that the soft mottled densities reached maximal intensity within two weeks resolution followed Miliary or somewhat larger fibrotic nodules were scattered diffusely throughout both lung fields on a film taken six weeks after onset and no further change was noted over the next six months

When seen six years later the patient was normal on physical examination Chest x ray revealed the former lesions to be calcified Many of the larger nodules had a dense calcific center and a lighter noncalcified periphery producing the halo effect often seen in the end stage of pulmonary histoplasmosis and because of this further examinations were made Sputum yielded no acid fast bacilli or fungi on smear and culture The histoplasmin skin reactions (1 1 000) were strong and positive whereas reactions to a coccidioidin skin test (1 100) and Mantoux test (1 1 000) were negative Complement fixation test for histoplasmosis using the yeast phase antigen of Histoplasma capsulatum gave positive results to a titer of 1 140

Other epidemics of acute diffuse pneumonitis essentially similar to this have been reported in none was the cause ever established One such epidemic was reported as Cave Sickness A New Disease Entity? Three epidemics were reported from the so called endemic area outlined for histoplasmosis which includes Tennessee Kentucky Arkansas Missouri and parts of Ohio Illinois Kansas Louisiana and Oklahoma A common feature was exposure to dust especially from habitations of pigeons chickens and rodents Histoplasma occurs naturally in dogs rats mice ferrets and horses and has been cultured from the soil where naturally infected rats have abounded Exposure to infected organic dust within the endemic area has led to pulmonary infection In the epidemic reported by the authors efforts to obtain the offending organism from the soil of the storm cellar were fruitless

Diagnosis of histoplasmosis in the generalized and usually fatal case is made by culture of sputum gastric contents bone marrow and lymph nodes removed for biopsy In the benign

and generalized abdominal soreness Physical examination gave normal results On the many cerebrospinal fluid examinations pressure was always elevated cells were almost exclusively lymphocytes count varied from 1 to 608/cu mm but was usually 100 Before therapy several smears and cultures showed Cryptococcus neoformans Sugar was 24 58 mg /100 cc usually 30 mg and chlorides 577 660 mg./100 cc usually 627 mg Globulin was increased

Conventional therapy was used at fir t In three week he received sulfadiazine aureomycin chloramphenicol and saturated potassium iodide solution but cerebrospinal fluid cultures continued to yield C neoformans Actidione® 20 mg intramuscularly and 20 mg intrathecally daily was started August 16 Culture of material taken the same day yielded C neoformans a culture taken 2 days later remained sterile for 30 d ys and other medications were gradually dis ontinued Intrathecal admini tration of actidione® was discontinued after two weeks because of pronounced signs of cerebral irritation 40 mg intravenously at bedtime was begun The actidione® supply was exhausted after 24 days and cerebrospinal fluid culture yielded the organi m 10 days later Two days later actidione® 60 mg daily intravenously was re umed and in four days cerebrospinal fluid cultures yielded no organisms

The patient went home without medication for a few days and returned 10 lb heavier and clinically improved but culture of cerebro pinal fluid again yielded organisms Since actidione® had inhibited but not eradicated the infection 500 mg aureomycin every six hours was given alone starting January 17 A culture then yielded C neoformans but two cultures thereafter were sterile so aureomycin was stopped after 23 days and resumed 8 days later A specimen of cerebrospinal fluid yielded a growth 26 days later while the patient was still on aureomycin Actidione® alone 40 mg intravenously daily was resumed March 22 The sample taken after a week remained sterile 30 days and cultures thereafter remained sterile except for 1 started on May 31 Daily intrathecal adminis tration of 20 mg actidione® was started in hope of eradicating the responsible foci by greater concentration in the cerebrospinal fluid After two days gait became ataxic and speech slurred there were pronounced lethargy and mental depression and the drug was discontinued He improved gradually and became asymptomatic in three weeks The drug was continued intravenously Subsequent cultures remained sterile and he was discharged the next January Culture of a specimen of cerebrospinal fluid obtained two months later was sterile without medication [Cell count and protein content of this fluid were not stated —Ed]

[Great caution must be exercised in accepting reports of beneficial effect of agents in torula meningitis The process may be one of great chron city lasting fo years with long asymptomat c periods To my knowledge there is still no reco ded instance of recovery with normal cerebrospinal flu d at the conclusion of the period of observat on —Ed]

lected cases) In some 10% of cases cryptococcosis has been diagnosed as *Hodgkin s disease* The histologic appearance of the reticuloendothelial or lymphatic reaction that occurs with cryptococcosis may in some cases be acceptable as Hodgkin s disease lymphosarcoma leukemia or sarcoid In some instances the *reaction* is a *granulomatous* lesion that may closely or remotely resemble such a specific diagnosis in others it is simple hyperplasia or chronic inflammation

For further investigation of possible relation between two specific diseases two series of patients were selected and cultures from sputum gastric aspirations lymph nodes and cerebrospinal fluid studied The experimental group consisted of 33 patients with histologically documented malignant lymphomas 15 of Hodgkin s disease and 18 of lymphosarcoma The 33 controls had a variety of nonlymphomatous diseases Positive cultures were obtained in six of the patients with lymphoma (table) and in one control (with pulmonary tuberculosis) Others should undertake such studies giving due consideration to whether two diseases coexist or whether the reticuloendothelial involvement is only part of systemic cryptococcosis

TYPE OF CRYPTOCOCCUS AND SITE OF RECOVERY IN 6 PATIENTS

CA E	DI GNOS S	O IGIN OF CULTUR	ORGANISM
1	Small cell lymph c m	Ce t al o y t m blood mes t c nodes spl e l e k l y te nal ma ow pe t ne l nd pe t d l fl d	C n fo m
		Lu g	C fo m ns a ocuon
2	G nt f ll le lymph s coma	Sp t m ga tr a p rat on	L ne forman
3	Hodgk d a e	B ne abd m al lymph odes	C e f rm ns ta nnoc ou
4	Hodgk n s d se s	Gast c a p t	C eofoema s af l oc o
5	Small cell lymph oma	G st c p at n	C n f m sa oc ous
6	G a t foll cl lymph a c m	G t c a p t n	C neofo ma s af n ocuou

Cryptococcus *Meningitis* (Torulosis) Treated with New Antibiotic, *Actidione*,* is reported by Henry M Wilson and Arthur W Duryea[7] (V A Hosp Alexandria La) There is no accepted effective therapy for this disease Patients are treated empirically and results are poor

Man 39 when hospitalized had vertigo malaise weight loss

(7) A M A Arch N of & Psy h t 66 470 480 October 1951

Artificial Transmission of Viral Hepatitis Among Intra venous Diacetylmorphine Addicts was observed nine times by Emanuel Appelbaum and Mennasch Kalkstein[9] (New York City) Spread of hepatitis or other viral infections among addicts has not previously been reported Addicts congregate in groups The diacetylmorphine is put into a tablespoon and tap water added Contents are brought to boiling point by a candle or match flame A small piece of cotton is put into spoon and the solution drawn up through cotton into a large medicine dropper Strips of paper are wrapped around the dropper tip to fit the needle After a tourniquet is applied to the arm the needle is inserted into an antecubital vein When the blood flow into the eye dropper is seen the tourniquet is released and the solution injected into the vein The hypo dermic outfit known as the works is never sterilized and is passed from one addict to another

Obviously this procedure lends itself to transmission of infectious agents Inevitably more cases of viral hepatitis will be added to those of transmitted malaria tetanus and bacterial and mycotic endocarditis heretofore recognized

Infectious Hepatitis Length of Protection by Immune Serum Globulin (Gamma Globulin) during Epidemics was studied by Joseph Stokes Jr John A Farquhar Miles E Drake Richard B Capps Charles S Ward Jr and Albert W Kitts[1] (Armed Forces Epidemiological Board) Epidemics in three relatively well segregated institutions were studied to determine (1) whether recent batches of gamma globulin were as effective as those first used (2) whether smaller doses to conserve supplies would be equally effective and (3) how long protection of the inoculated person would endure in the face of repeated exposure Results confirmed the effectiveness of recent batches of gamma globulin and of small doses (0 01 ml /lb) The outstanding finding was the duration of protection despite continued epidemic disease among control groups Single in jections gave protection for five eight and nine months in the three institutions It is conceivable but improbable that traces of gamma globulin remaining in the circulation or attached to tissue cells for these periods were responsible for such protec tion It is more likely that the waning passive immunity per

(9) J A M A 147 2 2 4 S pt 15 1951
(1) Ibid pp 714 719 O t 0 1951

Epidemic of Homologous Serum Hepatitis Apparently Caused by Human Thrombin is reported by Mark Falcon Lesses and Milton W Hamolsky[8] Human thrombin which has recently become commercially available is derived from pooled plasma and directly prepared from Cohn s fraction III 2 After Seitz filtration it is dried from the frozen state for distribution Clinically it has proved useful in controlling hemorrhage caused by extensive oozing The thrombin dis solved in isotonic sodium chloride solution immediately be fore use is used as such or placed in the interstices of a suit able matrix e g absorbable gelatin sponge (Gelfoam) Thrombin should be stored at refrigerator temperatures

Before Aug 23 1950 bovine thrombin was used as a hemostatic aid in operations at Beth Israel Hospital Boston The substitution of human for bovine thrombin passed un noticed until sudden occurrence of a number of cases of de layed postoperative hepatitis focused attention on its possi ble causative role Since then postoperative jaundice with the clinical and laboratory characteristics of serum hepatitis de *veloped in 22 patients The interval from use of the human* thrombin until appearance of symptoms was 66 136 days an incubation period entirely compatible with homologous serum hepatitis The patients were both private and ward surgical patients but there was no occurrence of the disease in patients on the private or ward medical services One or more trans fusions of whole blood was given 13 patients No plasma was used in any patient in this series Of those receiving trans fusions none was given blood from common donors Of 22 patients 7 had had neurosurgery chiefly laminectomy 8 had had cholecystectomy associated with excessive oozing of the gallbladder bed and 7 others had various types of operations Human *thrombin is not subjected to virucidal technics and* until these are available it should not be used therapeutically

[The list of circumstances under which hepatitis has been transferred from one human being to another grows more fascinating every year (See next article as well)—Ed]

(8) J A M A 147 727 730 O t 20 1951

Colbert Jr (Yale Univ) Luitgard Bungards and Marjorie Knowlton[3] (U S Army) The subjects were male enlisted personnel hospitalized within the first 10 days of onset of viral hepatitis Differentiation between infectious and serum hepatitis was not attempted Twenty four patients received 1 0 Gm aureomycin orally every 6 hours for 10 days Initially 10 received 50 mg chloramphenicol/kg body weight orally and then 500 mg every 6 hours for 10 days Terramycin was given orally to 20 patients in 1 25 Gm doses every 6 hours for 10 days Fifty four controls received placebos

Although gastrointestinal symptoms are difficult to appraise in viral hepatitis there was apparently some accentuation of the anorexia immediately after ingestion of aureomycin No significant alteration in the course was noted with use of aureomycin or chloramphenicol As compared with the control group results of liver function tests in patients receiving terramycin returned to normal more rapidly

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POLIOMYELITIS

Acute Poliomyelitis Differential Diagnosis of 409 Revised Diagnoses According to Katherine E Dawson Alfred C LaBoccetta Anthony S Tornay and Alexander Silverstein[4] the diagnosis of acute anterior poliomyelitis is at best only presumptive The early symptoms are nonspecific Headache fever sore throat diarrhea vomiting and malaise may be the cardinal complaints These are also present in many other febrile illnesses Examination of the cerebrospinal fluid is helpful but not diagnostic

In 1940-49 1 420 patients were admitted to the Philadelphia Hospital for Contagious Diseases with the diagnosis of acute anterior poliomyelitis Diagnosis was confirmed in 1 011 patients in 409 (28 9%) it was revised after clinical and laboratory evaluation The authors reviewed the 409 cases and obtained follow up histories to find information which might be of value in differential diagnosis

The diseases were classified on the basis of symptoms (1) nervous system diseases (113 patients 27 8%)—bacterial

(3) P S E p B l & M d 79 339 343 M h 195
(4) J P d t 40 71 84 J y 195

mitted inapparent or subclinical infections among the inoculated groups resulting in active immunity superimposed on passive immunity (passive active immunization) Results of animal viral studies in litters born to immune mothers and exposed to natural virus are compatible with such an explanation

Use of ACTH in Acute Viral Hepatitis James W Colbert Jr James F Holland Ivan Heissler and Marjorie Knowlton[2] report that over 4 000 patients with viral hepatitis were treated at the 98th General Hospital Munich in 1947 50 Investigation was started because of reports of effectiveness of ACTH against many diseases resistant to all therapy ACTH 25 mg was given every six hours intramuscularly to a total of 825 1 925 mg to each of five men then discontinued abruptly

Appropriate eosinophil response to ACTH was seen in each instance The most striking result was prompt return of appetite and energy Pruritus disappeared and although jaundice receded during treatment no definite change in liver size or tenderness was noted Serum bilirubin levels fell promptly and on cessation of ACTH therapy rose significantly in two patients Cephalin flocculation and thymol turbidity reactions did not follow so clear a trend althou h there were indications that ACTH contributed to their return to normal After withdrawal of the drug two patients experienced clinical relapse severer than the initial episode Anorexia nausea and abdominal cramps were accompanied by rise in total and one minute serum bilirubin levels and return to abnormal reaction to the cephalin flocculation and thymol turbidity tests In one of these patients again given ACTH within six hours nausea and abdominal discomfort vanished appetite became better and general improvement was noted Untoward effects were noted in all five patients with ascites sacral edema moon face and acne in four On withdrawal of ACTH four patients had joint pains particularly in the knees ACTH sensitization may have caused the arthralgia

[ACTH therapy of hepatitis is not generally being advised at present but might be resorted to in desperate situations —Ed]

Aureomycin, Chloromycetin® and Terramycin in Treatment of Acute Viral Hepatitis were assessed by James W

( ) New E gl d J Med 245 172 177 A g 2 1951

Available knowledge justifies conclusion that human feces derived from patients and healthy carriers is the most significant viral source in nature Since no evidence has been found of transmission of poliomyelitis by droplet nuclei there is no reason to advocate avoidance of crowds exclusion of children under 16 from movies churches or schools or exclusion of poliomyelitis patients or suspects from general hospital wards However it is reasonable during epidemics for individuals to keep fingers out of mouth and wash hands before eating keep flies away from all food and wash that which is consumed uncooked keep children under 16 out of crowded public wading and swimming pools and avoid intimate association with members of a family in which poliomyelitis has occurred within three weeks even though the patient has been removed to a hospital

[The data on which the conclusions are reached could not be included in the abstract but this appears to be a very sensible analysis of present day knowledge and should be helpful as a guide in answering the questions of worried parents —Ed]

Poliomyelitis Virus in Blood of Orally Infected Monkeys and Chimpanzees Viremia in human poliomyelitis has been demonstrated only once—early in the course of an abortive attack Other attempts have probably been unsuccessful because the viremia is transient and occurs early in the disease or in the incubation period Working on this premise Dorothy M Horstmann[6] (Yale Univ) infected 10 cynomolgus monkeys and 4 chimpanzees by a natural (oral) route with Brunhilde (Egypt) and Lansing (Y SK) type viruses and collected blood during the incubation period Seven of the cynomolgus monkeys and three of the chimpanzees were found to have viremia between the fourth and sixth days only It persisted in some animals over the entire three days but was not present in any after six days The interval between viremia and appearance of paralysis varied between three and seven days in the cynomolgus monkeys

This demonstration of poliomyelitis virus in the blood early in the incubation period in animals experimentally infected by the oral route with both Brunhilde and Lansing types is a new finding and suggests the possibility that viremia may occur in the incubation period of the human disease

[This seems to be a key contribution to our understanding of the pathogenes s of pol omyelit s —Ed]

(6) P oc Soc E p B l & Med 79 417 419 M h 1952

meningitis meningoencephalitis or encephalomyelitis Guillain Barre syndrome syphilis acute transverse myelitis brain abscess tumors tetanus lead poisoning acute porphyria tick paralysis and vascular lesions (2) peripheral nerve diseases (3) hysteria (4) respiratory infections—pneumonia or pneumonia with meningismus (5) musculoskeletal diseases (77 patients)—acute rheumatic fever (27), osteomyelitis osteoarthritis acute epiphysitis periostitis scurvy or trichinosis (muscle spasm due to trauma to bone muscle joint disease often caused symptoms suggesting poliomyelitis), (6) gastrointestinal diseases (in 17 patients physical examination was negative and cerebrospinal fluid normal but poliomyelitis was suspected because of diarrhea or vomiting) (7) genitourinary diseases (infants with acute infections of the urinary tract were often noted to have only fever and irritability) (8) acute febrile illnesses

[This study points up the important fact that a large variety of diseases may simulate early poliomyelitis We have seen erroneous diagnoses of poliomyelitis made in patients with osteomyelitis fracture rheumatic fever and many oth r acute infectious diseases —Ed.]

Transmission of Poliomyelitis Virus Albert B Sabin[5] (Univ of Cincinnati) analyzes the present state of our knowledge and the differing interpretations concepts and practical implications resulting from it

If the respiratory hypothesis is followed to its logical conclusion the greatest danger of infection would occur where large numbers of people congregate and not necessarily as a result of intimate association It would also follow that hospitalization of patients in general wards would be contraindicated and that school attendance during an epidemic would be fraught with danger Yet it is widely agreed even by adherents of the respiratory hypothesis that large gatherings involve no special danger If fecal contamination is the most important factor in transmission it is clear that ordinarily infection cannot be transmitted without touching someone or something contaminated and transferring the virus with the fingers to the mouth or swallowing contaminated food then the most likely epidemiologic prototype for poliomyelitis becomes bacillary dysentery It is also clear that in different circumstances various potential modes of transmission may assume special significance

(5) Chicago M Soc B 11 54 163 171 Sept 15 1951

with other diseases showed that *menstruation* was *present* 4 5 5 5 times more frequently in poliomyelitic women

Parturition in the acute phase of poliomyelitis increases risk of extending paralytic manifestations

Two speculations arise (1) that the pregnant host is more *susceptible to initial viral invasion* and *(2) that the woman* harboring the virus but showing no clinical evidence of disease becomes highly susceptible to invasion of the nervous system

The apparent role of sex pregnancy and menstruation in *increasing susceptibility to poliomyelitis in the adult* re emphasizes the possible influence of the sex hormones or other endocrine substances on the pathogenesis of this disease

Incidence of Normal Spinal Fluid in Acute Poliomyelitis is discussed by Edith E Nicholls[8] (Danville Pa) Indisputable cases of poliomyelitis are known to occur with a normal cytology but are not reported as poliomyelitis by many physicians and some hospitals unless evidence is manifested by paralysis and or increase in cerebrospinal fluid cell count In 320 poliomyelitis patients hospitalized from June 1944 through December 1949 a cell count of 10 or above and protein content of 60 mg or more were considered abnormal 64 *failed to show increases in either value in the first spinal tap* All of 43 patients (13 8 %) with normal fluid had definite evidence of poliomyelitis Repeated spinal taps are most important Fluids of 22 patients were normal but 61% were abnormal on second spinal tap Of 43 patients with normal fluids 34 *(79%)* had only one spinal tap and the rest *only* two Repeated taps often show bizarre and unpredictable *changes in the cerebrospinal fluid*

[A piece of information to remember —Ed]

***Arterial Hypertension Associated with Acute Anterior* Poliomyelitis** has been noted in over half the patients seen at the New York Hospital in the past two years Previous observations have implied that the hypertension has generally been associated with severe bulbar disease or respiratory insufficiency However *Fletcher H McDowell and Fred Plum*[9] found that it may not only be relatively common in acute *polio but may also be found in comparatively benign forms*

(8) J P d at 37 894 898 D mbe 1950
(9) New Engl J M d 245 41 45 A g 16 1951

Relation of Sex, Pregnancy and Menstruation to Susceptibility in Poliomyelitis was studied by Louis Weinstein W Lloyd Aycock and Roy F Feemster[7] (Boston) for evidence that inherent factors influence the course In 1949 and 1950 of 108 poliomyelitic women aged 20-40 26 (approximately 25%) were pregnant as compared with an expected 7% The threefold increase in expected incidence closely agrees with previous reports When checked to exclude preferential hos

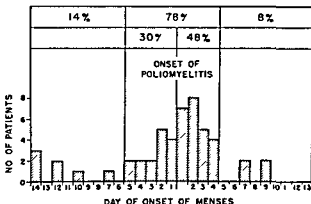


Fig 4—D y of t of m n lat on to t of p l myel t s sympt (C u t y f W t L *et al* N w E gl d J Med 245 54 58 J ly 12 1951)

pitalization of pregnant women sex distribution revealed that the younger age groups included considerably more males than females whereas among adults the shift was to female preponderance indicating that hospital admissions reflected actual sex distribution

Fifty women were closely questioned about onset of menstruation in relation to the first poliomyelitis symptoms and 78% had had menses five days before to four days after symptom onset (Fig 4) The incidence is striking and suggests possible importance of endocrine factors in provoking or hastening invasion of the central nervous system Change in ordinary length of intermenstrual interval was unrelated as no patient complained of early or delayed menstrual onset near the time of p yeliti ilar study of patients

(7) New E g[1]

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(8) J P d t 37 894 898 Decembe 1950
(9) N w E gl d J M d 45 41 45 A g 16 1951

Frequent blood pressure readings were taken on each of 95 patients and when a diastolic pressure above 90 lasted over 12 hours hypertension was recorded Though in the age group examined the expected incidence would be less than 9 1% 45 of the 95 adolescents and adults were hypertensive by this standard Of the 95 patients 86 had some paralysis The highest incidence occurred in those with bulbospinal paralysis or paralysis of all extremities Hypertension was greater and of longer duration in patients needing artificial respiration Of 30 patients requiring artificial respiration 29 were hypertensive in those who survived the acute phase average pressure was 164/104 and average duration had reached 98 days Ten patients still had hypertension 3 12 months after onset of illness In three patients with the Guillain Barre syndrome hypertension ranging from 160/100 to 230/160 developed while they were in the respirator but returned to normal when artificial *respiration was discontinued*

Arterial hypertension in these patients may have resulted from invasion of brainstem autonomic structures by poliomyelitis virus or may have been a manifestation of a generalized alarm reaction Anoxemia hypercapnia or artificial respiration appeared to intensify and prolong the otherwise transient hypertensive state

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MISCELLANEOUS VIRUS INFECTIONS

Outbreak of Psittacosis (Ornithosis) from Working with Turkeys or Chickens Parakeets and pigeons apparently have accounted for most of the psittacosis in the United States canaries chickens and ducks have also been incriminated but it seems likely that the importance of common barnyard birds in the spread of this disease has been overlooked J V Irons Thelma D Sullivan and Joyce Rowen[1] (Austin Tex) describe salient epidemiologic clinical and laboratory findings in an outbreak attributed to working with turkeys and possibly even with chickens There were 22 cases (30%) of psittacosis among 78 workers at a poultry and egg plant All patients had been killing *picking feathers from or wrapping* heads of turkeys The clinical picture ranged from mild influ

(1) Am J P b H lth 41 931 937 Aug 1 1951

enza like attacks to grave illness and three deaths Serums obtained late in the course of the disease invariably showed significantly high complement fixation titers with Lygranum® antigen (table) It was concluded that discharges from a

DISTRIBUTION OF LYGRANUM® TITERS IN SERUM OF PATIENTS AND OF PERSONS PRESUMABLY EXPOSED BUT NOT ILL

Titer	Ill	Not Ill
1 20	0	3
1 40	5	3
1 80	5	0
1 160	5	2
1 320	3	0
Total	18	8

group of turkeys constituted the most probable source of infection it seemed most doubtful that infections had been acquired from chickens

Primary Herpes Simplex Virus Infection of Adult Infection commonly occurs in infancy usually manifested as acute stomatitis According to Burnet and Williams the primary infantile infection is followed by latent persistence of virus in the tissues activated at times and recurring in the form of vesicular lesions of the lips or other sites invaded during the primary infection

Primary herpetic infection of the adult has been only rarely described Edwin D Kilbourne and Frank L Horsfall (Rockefeller Inst) report cases of infection associated with disease dissimilar to that identified with the childhood infection and summarize existing knowledge of primary infection of the adult

Primary herpes simplex virus infection in the adult may be associated with disease of the mouth throat cornea genitalia skin or central nervous system Stomatitis resembles the infantile disease and is accompanied by fever and malaise The probable herpetic origin of acute keratitis has been established by isolation of the virus The virus has also been recovered from cutaneous lesions of patients with Kaposi s varicelliform eruption and from vaginal ulcers of patients with primary genital infection Herpes virus infection has been implicated in benign lymphocytic meningitis and in fatal encephalitis

(3) A M A Arch Int Med 88 495 502 Oct 1951

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(1) Am. J P b H 41 931 937 A gu t 1951

found 18 months previously The virus could not be isolated from mice caught in five other areas of the city

Diagnosis and Immediate Prognosis of Japanese B Encephalitis Observations Based on More Than 200 Patients with Detailed Analysis of 65 Serologically Confirmed Cases By the end of 1950 Japanese B encephalitis was the only endemic entity to reach significant proportions among American troops in Korea This virus disease transmitted by the mosquito especially culex appears annually in late summer and early fall Robert B Dickerson Joseph R Newton and James E Hansen[4] (M C U S A) observed 228 of 299 patients with the disease Of these 110 were hospitalized for a minimum of eight weeks and made up a clinically homogeneous group but results of complement fixation tests were positive in only 65 These form the basis of the data in this report

Typically onset was rapid but not sudden with a two to four day interval between the prodrome of fever headache and chills and development of full blown meningeal signs Headache was the presenting symptom of 80% of patients and occurred in all as did fever (temperature usually rose over 104 F) which reached a peak in two to four days and subsided gradually over five days Nuchal rigidity was found in all but was not a particularly disturbing symptom Vomiting was common Characteristically the patients had immobile and expressionless facies diminished blinking and cogwheel like eye movements Generalized paresis was a constant feature being present before hospitalization in most patients and reaching a peak in five or six days Localized paresis was noted in 31% about half having multiple localizations The arms were most commonly involved Mild incoordination was noted in half of the patients but a moderately coarse tremor accentuated by fatigue and intention was seen in 90% During convalescence gait was stiff and without arm swinging in a third Only 10 patients were not confused during the acute phase and many had amnesia for a portion of the course Many complained of well demarcated (to the patient) numb places as they regained mental clearness Weight loss even in patients with milder cases was striking averaging 26 lb

After 10 weeks 12 patients had significant residual func

(4) Am J M d 12 77 33 M h 195

The first two cases reported here add further evidence that primary herpes simplex virus infection of the adult may be associated with clinical disease of variable nature distinctly *different from the acute gingivostomatitis characteristic of* infantile infections Notably both patients were suspected of having infectious mononucleosis Since the herpes simplex virus was recovered on three occasions from recurrent aphthous ulcers in the third patient herpes simplex virus infection may therefore account for some instances of recurrent aph*thous ulceration and cannot be flatly rejected as an etiologic* agent of this process

Lymphocytic Choriomeningitis Review of 10 Cases P R Duncan A E Thomas and J O H Tobin[3] (Manchester) observed the 10 cases in six months In all serologic methods indicated the cause and in four the virus was isolated Three clinical syndromes in man have been attributed to the virus of lymphocytic choriomeningitis (1) meningitis the type most often described (2) encephalomyelitis and (3) an influenza like infection without apparent nervous system involvement In the present series all were cases of meningitis except one a laboratory infection Symptoms suggesting a virus infection appeared 7 21 days before onset of meningitis in eight patients in the ninth they lasted 3 days They included general malaise pains in the back and limbs shivering sweating and striking anorexia Lymphocytic meningitis may also develop in poliomyelitis virus encephalitis mumps Bornholm disease herpes simplex lymphogranuloma venereum syphilis Weil s disease canicola fever torulosis toxoplasmosis mastoid disease and cerebral abscess The two conditions that confused the diagnosis were tuberculous meningitis and glandular fever Presence of premonitory symptoms resembling influenza and occurrence of a brief remission before onset of meningism support a diagnosis of lymphocytic choriomeningitis Presence of mice and knowledge that other cases have occurred in the immediate neighborhood may be of value All but two patients in this series came from two localized areas in Manchester Four lived or worked within 200 yd of each other the other four within 400 yd Infected mice were caught in one patient s house which was only 70 yd from the one where mice harboring the virus had been

(3) Lancet 1 956 959 Ap 8 1951

[This should be an important reference article for the clinical picture of this disease —Ed]

Clinical Evaluation of Aureomycin and Chloramphenicol in Herpes Zoster Edward H Kass Robert R Aycock and Maxwell Finland[5] compared results in three groups of patients one treated with aureomycin a second treated with chloramphenicol and a third in which antibiotics were withheld and a simple analgesic agent was given Seventy two patients were selected at random from the outpatient department admitting floor or wards of Boston City Hospital between September 1949 and July 1951 and all were seen again in July or August 1951 for final follow up study Each patient was told that he was receiving a new expensive medicine that was usually effective and was then given the number of capsules or tablets needed until the next visit He was requested to return all unused medication at the end of the week

Results did not support earlier impressions that aureomycin and chloramphenicol favorably alter the course of herpes zoster They and those of Carter indicate that contrary to common belief most patients recover fairly promptly and without complications Only 18% of the patients had post herpetic neuralgia Lesions cleared within two weeks after their first appearance in over 75% of the patients and pain was completely relieved in less than two weeks in over 50% irrespective of the type of therapy used

[It is interesting that an attempt to evaluate a therapeutic agent brought realization that most cases of herpes zoster resolve rather promptly without sequelae —Ed]

RICKETTSIAL INFECTIONS

Q Fever in California VII Clinical Features in 180 Cases are discussed by William H Clark Edwin H Lennette Oscar C Railsback and Mary S Romer[6] (Berkeley Calif) In general only the more severe infections were seen during the early part of the studies Each case satisfied one or more of the following diagnostic criteria (1) demonstration of the causal rickettsia in the blood during acute illness (2) dem

(5) N w E gl d J Med 246 167 17 J 31 1952
(6) A M A A h I t M d 88 155 167 A g t 1951

tional losses especially of a mental nature Some evidence of upper and motor neuron damage was noted and there was one instance of facial palsy The latter was greatly improved at 12 weeks Intellectual impairment and confusion characterized patients who became psychotic All had delusions but hallucinations were not noted Generally patients without gross evidences of mental deterioration did not show significant deviation from previously attained scores when retested by Army classification examinations In retrospect the authors believe that presence of the Babinski reflex indicated a poor prognosis being found but once unrelated to later residual changes or death Likewise prolongation of fever was an unfavorable factor All patients febrile for 11 or more days had residua or died

Ninety per cent of the patients had initial counts of 20 400 cells/cu mm cerebrospinal fluid Early in the disease about 30% of the cells were polymorphonuclear Only two patients had cell counts in excess of 1 000 In almost all pleocytosis persisted through seven weeks of follow up Chloride and sugar levels were normal whereas initial protein levels were slightly elevated Initially peripheral blood usually contained 10 000 19 000 white cells Slight elevation persisted for about four weeks Specific complement fixing antibodies developed after four weeks in only 20% of patients were they at diagnostic levels at the end of three weeks

It was concluded that the most significant physical changes in Japanese B encephalitis are altered sensorium masklike facies thick slow speech coarse ocular tremor relatively symmetrical neurogenic paresis without corresponding sensory lesions or paralysis and normal or increased deep tendon reflexes and/or abdominal reflexes barring profound depression of vital functions Presence of four of these signs can probably be regarded as pathognomonic of the Japanese B encephalitis syndrome

Despite lack of specific therapy the 10% mortality among the troops was about a third that of the natives This was attributed to supportive care especially maintenance of an adequate airway The immediate cause of death was bronchopneumonia pulmonary congestion and edema and interference with pulmonary ventilation rather than primary failure of the respiratory mechanism

Splenomegaly was noted in seven and splenic tenderness in four patients

Of 102 serologic tests for syphilis with the usual and cardiolipin antigens 68% of the results were positive White cell counts were performed on about half the patients During the first week of illness total count ranged from slightly depressed to slightly elevated later in the illness however a significant proportion of patients had counts above the normal range Either complement fixing or ag glutinating antibodies were demonstrable in serums of all patients Chest x rays were made of 65 patients 20 of whom had more than one of 89 roentgenograms 69 were normal and 20 taken of 18 patients showed infiltrative lesions Thus of the group studied 28% had infiltrative lesions at some time during the illness

Most patients were febrile for 3 weeks or less mean duration of fever was 16 3 days and median 12 5 days Nevertheless it should be noted that 30 patients (17%) were febrile for four weeks or longer The occurrence of severe and protracted illness in a considerable proportion of persons with Q fever is of some interest since Coxiella burnetii infection is usually thought to produce a mild and self limited disease in most instances The more prolonged illnesses occurred more often in patients 40 or over Duration of febrile illness alone however does not represent the entire course Pa tients aged 40 or over were weak easily fatigued and some times mentally depressed for long periods after fever had subsided

Prognosis for life is excellent In this series no patient died of Q fever There is no unequivocal evidence that a chronic infection with C burnetii may occur

Brill s Disease IV Study of 26 Cases in Jugoslavia Previous reports have dealt with the entity occurring in immigrants to nonendemic areas To test the theory that it is a recrudescence of typhus in the absence of reinfection Edward S Murray Tadija Psorn Predrag Djakovic Stanko Sielski Vilim Broz Franjo Ljupsa Jakob Gaon Rade Pavlevic and John C Snyder[7] sought cases in Jugoslavia where epidemics have occurred Physicians in eastern Bosnia

(7) Am J P b H lth 41 1359 1369 N mb 1951

onstration of a fourfold or greater rise in complement fixing or agglutinating antibody titer during illness and convalescence (3) demonstration of a high complement fixing or agglutinating titer without subsequent rise, together with history of recent (within two months) illness clinically compatible with the diagnosis of Q fever (serum antibody titers of 1 32 were considered significant)

Onset was sudden in 72% of the cases Fever was constantly present the temperature exceeding 102 F at some time during the clinical course initial temperature was commonly 104 106 F and occasionally continued for weeks Elevated temperature of variable degree persisted from two days to as long as three months but temperatures above 102 F were uncommon after the third week All patients complained of chills and 74% had true shaking rigors on one or more occasions

Severe headache was a prominent symptom muscular aching was less common and stiffness of the back or neck severe enough to suggest meningeal irritation was observed in 5% of the patients Symptoms and signs relevant to the respiratory system were rare although these and pulmonary involvement have often been used as the principal diagnostic criteria in Q fever Cough was present in about a fourth of the patients it was rarely severe and was almost never an initial complaint Chest pain was noted by 10% was generally pleuritic and usually associated with demonstrable pulmonary lesions Crepitant rales were heard at some time during illness in 21% The relative infrequency of symptoms and physical signs referable to the respiratory tract resulted in the roentgenographic study of only a few persons Roentgenograms were made for 65 patients and pulmonary abnormalities were found in 22 (34%) Among the gastrointestinal symptoms anorexia of varying degree was the commonest complaint Hepatomegaly and liver tenderness were surprisingly common being observed in 11 and 7% respectively Jaundice reported by Derrick in his original description of the disease was observed in 5% Until it was recognized that such evidence of hepatic involvement was consistent with the diagnosis of Q fever these cases gave rise to considerable difficulty in clinical differentiation from infectious hepatitis

Splenomegaly was noted in seven and splenic tenderness in four patients

Of 102 serologic tests for syphilis with the usual and cardiolipin antigens 6 8% of the results were positive White cell counts were performed on about half the patients During the first week of illness total count ranged from slightly depressed to slightly elevated later in the illness however a significant proportion of patients had counts above the normal range Either complement fixing or ag glutinating antibodies were demonstrable in serums of all patients Chest x rays were made of 65 patients 20 of whom had more than one of 89 roentgenograms 69 were normal and 20 taken of 18 patients showed infiltrative lesions Thus of the group studied 28% had infiltrative lesions at some time during the illness

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were informed of the entity as it is found in the United States and asked to report all cases of fever and severe intractable headache in patients with a history of typhus Each such patient was seen promptly by Murray or Snyder

Of the 38 patients reported 26 had rickettsial agglutination titers of over 1 200 or more than fourfold rises on serial specimens They were aged 9 56 14 were male That 21 patients had had an earlier attack of typhus (in 1938-45) seemed certain from their accounts Nineteen patients were hospitalized All had severe intractable headache this was the most characteristic single feature of the disease Nine had a rash Fever lasted less than 6 10½ days (average 8½) There were no deaths Twenty three had rickettsial agglutination titers of 1 800 or higher 12 20 days after onset the other three had titers of at least 1 400 Control titers never rose above 1 100 None had a titer of 1 160 in the Weil Felix reaction the level generally considered diagnostic

The authors believe that these were not cases of epidemic louse borne typhus because no evidence of louse transmission was obtained no secondary cases were found *second attacks are rare and most of these patients gave a definite history of a previous attack the clinical course was short and mild only half had a characteristic rash and the Weil Felix reaction was consistently negative whereas in epidemics of louse borne typhus it is positive in over 90% of cases* Brill himself noted this lack of a positive Weil Felix reaction

It was concluded that the 26 patients had Brill s disease Identification of Brill s disease in a typhus zone adds further support to the theory that man is the interepidemic reservoir of epidemic louse borne typhus fever

[Evidence continues to accumulate in favor of Zinsser s hypothesis that *Brill s disease is a recrudescence of typhus after a free interval of many years* —Ed]

AMEBIASIS

Chronic Amebiasis A Common Disease With an estimated 10-20 million persons in the United States suffering from chronic amebiasis it ranks as a common chronic disease Robert G Lehman and Leonard R Thompson[8] (San

(8) A Wet Med & S g 5 755 758 S pt mbe 1951

Pedro Calif) observed 238 cases over 34 months Although the infection is localized mainly in the colon it is a mistake to consider the diagnosis only in dysentery patients Only the cysts are infective and these are usually found in solid *stools whereas the short lived trophozoites are frequent* in liquid feces Thus the healthy carrier rather than the acutely dysenteric patient is the transmitter After oral in gestion the cyst disintegrates in the lower intestine and releases one to four motile trophozoites which are responsible for the pathologic changes and the symptomatology After a period of activity and multiplication the trophozoites become encysted and pass out in feces The clinical picture ranges from that of the asymptomatic carrier through various de grees of dysentery to the more severe instances of liver abscess In temperate and colder regions the milder infections are commonest and least often diagnosed Abdominal pain occasionally severe is periodic in most infected persons It may be sustained or paroxysmal There is no characteristic localization and often acute appendicitis must be excluded In one series of 100 amebiasis patients nearly a third had been referred for appendectomy When the pain is paroxysmal it is frequently diagnosed as chronic appendicitis However in amebiasis the associated symptomatology is usually absent Similarly cholelithiasis irritable colon and peptic ulcer are often erroneously considered

Neuromuscular symptomatology is common and often leads to incorrect diagnosis of psychoneurosis Headaches often persisting through the day drowsiness faulty memory lack of ambition irritability myalgia and legache are com mon in chronic amebiasis The authors have found that cir culatory symptoms are not outstanding although arrhythmias labile pulse tachycardia and palpitations are said to be common

[The authors do not give details of the method of making a diagnosis of symptomatic amebiasis The implication is that the diagnosis was only made when parasites were found in the feces The catch is of course that most people harboring amebas are probably asymptomatic carriers The authors estimate that 10 000 000 20 000 000 persons in the United States are suffering from amebiasis This seems to ignore the concept of the asymptomatic carrier Doubtless some individuals may have vague ab dominal symptoms but as the authors themselves adm t at one point amebiasis even when present may not be the cause of the patient s com plaints They do not state how frequently they were able to relieve symp toms by administration of ant amebic therapy —Ed]

Amebiasis Common Clinical Problem It is estimated that 5 20% of the American population harbor the Endameba histolytica *in their* intestines Most carriers rather than being *symptomless* actually have low grade digestive symptoms relieved after appropriate therapy T Haynes Harvill[9] (Dallas) points out that infestation with E histolytica more often produces vague constitutional complaints acute dysentery is the exception rather than the rule

The irritable colon syndrome typical of complaints often encountered includes *bowel irregularity* usually with constipation occasionally alternating with mild diarrhea it is associated with the intermittent passage of moderate to profuse amounts of mucus in the stool There is usually no history of true dysentery Other complaints are lassitude fatigue irritability capricious appetite and all the vague and *nondescript symptoms commonly* labeled neurasthenia

Some patients have true amebic hepatitis which may progress in a more severe form to amebic abscess of the liver This hepatitis is characterized by tenderness of the enlarged liver on deep pressure or fist percussion Later there are reduction of excursion or complete *immobilization of the right* side of the diaphragm *slight icterus* elevation of the white blood cell count and fever

Diagnosis of amebiasis depends on demonstration of E histolytica in the stool specimen Complement fixation tests and amebic stool culture have not been of great clinical value *Unfortunately few practicing physicians* or laboratory technicians are proficient in stool parasitology

Sigmoidoscopy usually reveals normal rectal mucosa X ray examination of the colon with barium enema may reveal shallow ulcerations in the cecal region manifested by feathered *irregular margins of the cecum on the film* taken with the colon filled with barium Rarely there may be an annular granulomatous mass simulating carcinoma A third finding of presumptive but not diagnostic value is conical narrowing of the cecal tip associated with ready reflux of barium into the terminal ileum *Often the barium enema examination reveals* no abnormalities

Because of these factors and the relative lack of toxicity of amebacidal drugs a therapeutic trial of antiamebic medica

(9) Tex x J Med. 48 4 7 J n y 195

tion often has practical clinical value Emetine because of its toxicity has no place in treatment of chronic low grade colonic amebiasis It is used primarily for acute dysentery and amebic hepatitis

Vioform® diodoquin® and yatren® constitute the iodoxy quinoline group of amebacidal drugs Vioform® is believed to be the best tolerated and to give the most satisfactory results Dosage is 250 mg three or four times daily for 10 14 days

Carbarsone 250 mg two or three times daily for 10 days is advocated by some Arsenicals should not be used in the presence of severe liver or kidney damage or known intolerance to arsenic Since slight cramping and loose stools may occasionally accompany treatment carbarsone is a poor drug with which to begin therapeutic trial

Chloroquine an antimalarial is recommended for hepatic amebiasis Its therapeutic effect results from a concentration 500-600 times in the liver It has no great effect on intestinal amebiasis

Aureomycin bacitracin and terramycin are reported to have pronounced antiamebic effects Their primary action may be the eradication of intestinal bacteria the presence of which seems necessary for the growth and multiplication of ameba Their expense precludes widespread use unless their therapeutic success is shown to be significantly greater than that of the older remedies

When receiving a therapeutic trial of antiamebic medication the patient is informed that his symptoms may be due to amebiasis although the parasite has not been demonstrated in stool examinations He is given a 10 day course of vioform® exclusive of other therapy and told that this may not relieve his symptoms After the 10 days if unequivocal improvement is noted a 10 day course of carbarsone is given followed by a repeated course of an iodoxyquinoline

[This appear to be a more critical approach to the ameb a is p ob lem The views expressed are in accord with those of other competent authorities and it is probable that a s gnificant number of ca es of low grade illnes due to amebiasis could be detected and helped by a program such as that outlined here —Ed]

Treatment of Hepatic Amebiasis with Chloroquine is discussed by Roger Lane[1] The finding or failure to find End ameba histolytica in a stool specimen is of limited diagnostic

(1) J T p M d 54 198 06 O t b 1951

value because if present they may be no more than harmless saprophytes and even when gross amebic disease is present repeated examinations may fail to produce a positive result Ochsner and DeBakey reviewing over 4 000 cases of hepatic involvement in the literature stated that in only 11 6% were stools positive *this is about the figure for the normal population* The great difficulty in preparing a potent antigen has made the complement fixation test unreliable although it has been found more reliable in hepatic than in intestinal cases The diagnostic value of sigmoidoscopy in chronic diarrhea is undoubted *often amebas can be found only from an ulcer* scraping In true liver abscess leukocytosis is almost invariable but is often absent in chronic forms and in the preabscess stage

Treatment is generally agreed to be required only for those suffering clinically from tissue invasion as soon as this diagnosis has been established a full combined course of treatment should be undertaken High percentage of relapses after emetine by injection has caused it to be abandoned as the sole drug particularly in patients with the intestinal type *Many adjuvant drugs in different combinations* have been suggested It is now clear that clinical improvement *with massive doses of penicillin and with aureomycin* is due solely to their effect on the secondary bacterial invaders and that antibiotics are as ineffective on the ameba *in vivo* as they are *in vitro*

Chloroquine for hepatic amebiasis has had conspicuous success It is almost completely absorbed from the upper intestinal tract and slowly excreted disappearing by degradation at about 60% per week after administration is stopped Its conspicuous characteristic is its concentration inside various cells most important of which are the liver cells and leukocytes at a rate of 200 500 times that in the plasma Many rapid cures of large liver abscesses and even of such severe complications as pleural or peritoneal rupture have been reported Average dose is 600 mg of the base daily for two days 300 mg for 10 days then either 150 mg daily for two to three weeks or 600 mg weekly for a month There is a tendency to relapse but a second course usually effects rapid cure The drug is usually supplied as the monosulfate or diphosphate a tablet of either represents 150 mg of the base

Lane gave chloroquine to 20 consecutive patients with hepatic amebiasis One group was treated with chloroquine alone another with chloroquine after emetine and a third with a later addition of emetine Results of treatment are shown in the table

Only extensive clinical trials in every area in which amebiasis is endemic can disclose the proper place of chloro

RESULTS OF TREATMENT

	CH O- QU E O	CH ORO- QUI PT LM	EM TI & CH O- QU
Disappearance of symptoms			
Liver tenderness			
< 7 da	9	1*	–
7 14 da	3	1†	1
> 14 da		2†	3
Abdominal signs			
< 7 da	1	1	–
7 14 da	3	1	2
> 14 da		2	2
Time off work			
None	5	–	1
< 7 da	6	1	–
7 14 da	1	3	3

P t t t t d l wh t m tte tly t m ng l g f om sta t f chl oq n th t f om t t f y t tm t
†T tm t n t mpl t d n on

quine in treatment Advantages over previous amebacides are that it can be taken orally is cheap administration requires only intermittent medical supervision toxicity is usually low and it does not interfere with any normal occupation

Arthritis Due to Intestinal Amebiasis Postwar incidence of amebiasis has focused attention on extraintestinal manifestations including symptoms due to hematogenous spread of the ameba and toxic symptoms arising from the primary intestinal focus Toxic symptoms include headache arthralgia backache neuralgia anorexia weight loss and fatigue Chronic arthritis due to amebic infection has rarely been mentioned as a toxic symptom Emanuel M Rappaport A Y Rossien and Louis A Rosenblum (New York City) discuss its occasional occurrence It is clinically indistinguishable from chronic rheumatoid arthritis but unlike the latter responds rapidly to specific therapy Four cases of recurrent

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polyarthritis associated with mild gastrointestinal symptoms of amebic origin are reported Institution of amebacidal therapy led to rapid cure of both intestinal and arthritic complaints

Amebic arthritis usually takes the form of polyarthritis and is subject to spontaneous remissions and exacerbations The main obstacle in diagnosis was the relatively insignificant gastrointestinal symptoms with arthritic complaints predominating One patient never had diarrhea in another arthritis appeared two years after the last attack of diarrhea Diagnosis of amebic arthritis was established by isolation of ameba from the stools and subsequent rapid response of the arthritis to amebacidal therapy Previous reports indicate that many clinical phenomena resulting from amebic infection were due to secondary invasion of the ulcers by bacterial pathogens If true arthritis would be commoner in chronic amebic dysentery with extensive ulceration in which secondary infection is an almost invariable accompaniment Actually arthritic complications are most frequent in nondysenteric amebiasis The authors suggest that amebic arthritis is the result of sensitization to Endameba histolytica or its by products The combination of urticaria and arthritis in one patient was highly suggestive of such response to absorption of an intestinal toxin Though amebic arthritis is probably rare examination of stools for E histolytica is indicated for all patients with 'rheumatoid arthritis with concomitant gastrointestinal disturbances

[The case reports in the original article are impressive —Ed]

PARASITIC INFESTATIONS

Trichinosis Observations on 50 Sporadic Cases consecutively hospitalized over a five year period were made by Edward Wasserman[3] (Boston City Hosp) In only 36% was initial diagnosis correct Acute glomerulonephritis influenza meningitis rheumatic fever sinusitis and gastroenteritis had been diagnosed in most of the others At least 50 diseases have been confused with trichinosis which is particularly widespread in America where autopsies indicate that every

(3) Connecticut M J 15 965 969 November 1951

sixth person is infected Trichinosis is an acute disease resulting from the ingestion of pork products infected with the encysted larvae of the nematode Trichinella spiralis Symptoms appear in 2 28 days and occur in three stages The initial (gastrointestinal) phase involves development of parasites in the digestive tract after dissolution of the cyst After copulation the female penetrates the mucosa to deposit eggs

MAJOR SYMPTOMS IN 50 CASES OF TRICHINOSIS

	%		%
Fever	96	Abdominal pain	36
above 101 F	74	Anorexia	30
below 101 F	22	Chills	24
Muscle pains	68	Cough	14
Swelling of eyelids	66	Sweating	14
Nausea	54	Stiffness of neck	12
Weakness	50	Diplopia or blurring	6
Headache	46	Constipation	6
Vomiting	46	Rash	4
Malaise	40	Neurologic changes	4
Diarrhea	38	Epistaxis	2

The young parasites enter the lymphatics a few days later and are carried throughout the body in the second phase of toxicity Larva encystment in muscle tissue constitutes the third phase Eosinophilia is the most constant and significant finding early in the disease and generally appears before the end of 14 days rising thereafter Leukocytosis is common but not invariable Typically the disease is characterized by fever swollen eyelids and muscular pains but the possible symptomatology is extensive (table) Neurologic complications may be misleading and trichinosis should be considered in vague cases When taken electrocardiograms were abnormal in 19 4 per cent in this series The abnormalities were transient and included inverted or low T waves low voltage and conduction defects Since larvae do not encyst in cardiac muscle the cause of these changes is unknown but may be direct invasion of the myocardium by larvae or by blood borne toxins Gastrointestinal symptoms have been reported as infrequent but the authors found them in some form in all but 10 of their patients

The incidence of histories positive for pork ingestion will rise if the examiner questions patients about such pork containing foods as hamburger and sausage Although other animals have reportedly been infected the pig is the main

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(3) Connect cut M J 15 965 969 N embe 1951

improvement with complete freedom from symptoms after the second day Temperature declined to normal within 48 hours with occasional low grade elevations thereafter

Frequent blood counts failed to demonstrate any spectacular fall in number of circulating eosinophils The first course of cortisone caused a gradual decline in the total white blood cells and proportion of eosinophils During the second course the fall of eosinophils was less striking

Skin tests with 0 02 cc trichinella extract were repeatedly negative for immediate or delayed reaction on four occasions from the 2d to the 27th hospital days Since it was felt that cortisone might have altered the result a skin test was repeated nine days after cortisone was discontinued at which time a positive immediate reaction was obtained

Treatment of Human Ascariasis with Hetrazan ® Use of Sirup Containing 1 Diethylcarbamyl-4 Methyl Piperazine Dihydrogen Citrate (Hetrazan®) Ascaris lumbricoides has been said to be one of man s most constant companions from time immemorial and it was predicted that modern plumbing would eventually dissolve the partnership However as plumbing facilities are not yet available to most of the 2 000 million inhabitants of the world this is not likely for some time

Elmer H Loughlin Irving Rappaport Aurele A Joseph and William G Mullin[5] point out that in addition to nutritional deficits ascaris can produce seriou reactions Migration of the larvae through the lungs causes hemorrhages and even hemorrhagic pneumonia which may prove fatal In the intestinal tract the adult ascarides when numerous and irritated may ball up and cause intestinal obstruction At times they find their way into the appendix bile ducts and liver and may travel through the stomach to emerge from the mouth nose and auditory canal

Anthelmintics for ascariasis have been limited to a few preparations Oil of chenopodium is effective but like santonin is toxic the toxicity of both is usually augmented by the patient s poor physical condition Hexylresorcinol produces no major systemic signs of toxicity but is available only in hard gelatin capsules and therefore difficult to administer to small children If the capsules are chewed or broken in the mouth chemical burns of the buccal and esophageal mucous membranes will ensue For maximal effectiveness all of these

(5) L t 2 1197 1200 D 29 1951

host Rats have a high incidence of infection and serve as a secondary reservoir because of their cannibalism and ingestion of pork scraps No practical method of detecting infected pork has been discovered Adequate cooking involves heating all portions to 131 F Freezing to be effective has to be done at 5 F for 20 days or 0 F for 1 day Pickling and smoking are effective

Cortisone Treatment of Trichinosis Edgar Rosen[4] (V A Hosp Oakland Calif) reports a moderately severe case in which cortisone caused outstanding improvement

Man 42 became ill 14 days before hospitalization with generalized myalgia headache chilly sensations feverishness frequent drenching sweats drowsiness diarrhea and thick productive cough. Diarrhea ceased after the third day The fourth day he began having chills nausea and vomiting sore throat external swelling of the neck periorbital edema conjunctivitis and photophobia One week before onset of illness he had ingested 2 or 3 oz uncooked pork sausage The history was essentially negative except for a duodenal ulcer inactive in recent years Physical examination revealed an acutely ill febrile man who held himself stiffly because of diffuse muscle soreness The tongue was slightly reddened and there was a cluster of petechiae in the center of the hard palate There was moderate tenderness on fist percussion over the lumbar spine tendon reflexes were hypoactive

White blood cell count was 14 000 with 50% polymorphonuclear leukocytes 11% band forms 6% monocytes and 33% eosinophils An ECG showed a vertical heart position with clockwise rotation, low voltage of QRS complexes in all leads and diphasic to shallowly inverted T waves in leads reflecting the epicardial surface of the left ventricle These changes were interpreted as compatible with trichinous myocarditis A second ECG taken six days later was essentially normal Muscle biopsy revealed numerous foci of inflammatory cells including eosinophils Hyaline degeneration and fragmentation of muscle fibers were noted and one section revealed a large inflammatory focus containing an S shaped portion of a trichina without any definite capsule formation

Combined antibiotic therapy—penicillin and terramycin—for four days gave no evident benefit Cortisone was then given (700 mg in 4 days) temperature fell dramatically and after 48 hours he was asymptomatic except for persistent slight cough and minimal muscle soreness To furnish evidence that this improvement was related to the treatment cortisone was discontinued for four days The general condition rapidly deteriorated Cortisone therapy was resumed and continued for 14 days There was remarkable

(4) Am J M Sc 223 16 19 J a y 1952

negative anaerobic nonsporulating bacterium The tendency has been to consider these organisms when isolated from blood or suppurative lesions as nonpathogenic contaminants However in five years Leon V McVay Jr and Douglas H Sprunt[6] (John Gaston Hosp Memphis Tenn) observed 35 cases of bacteroides infections They believe that many serious septicemias of unknown cause especially those following intestinal or genitourinary surgery are due to bacteroides

Of the 35 patients 21 were critically ill and 11 died Bacteroides organisms were the primary cause of death in *nine and were secondary invaders in two patients with cancer* Patients were aged 7 months to 71 years 24 were female 30 were Negro Interestingly most did not appear as ill as the clinical course indicated Although patients often had a very high fever (e g 106 F) with severe leukocytosis symptoms were frequently minimal This was noted in three patients with septicemia two of whom died The usual clinical picture was that of a pyogenic infection predominating symptoms being determined by the portal of entry (respiratory tract gastrointestinal tract genitourinary system auditory system or skin) The characteristic pathologic lesion was that of localized suppuration similar to that caused by staphylococci which at times extended to invade the blood stream with subsequent bacteremia or septicemia and metastatic abscess formation

The patients were classified on the basis of portal of entry Thus in six the infection originated in the respiratory system All were critically ill and had spiking fever Leukocytosis was present in five Three died The gastrointestinal tract was the portal of entry in six Again all were critically ill Four died All were icteric in five hepatic abscesses were found at autopsy or surgery One patient responded dramatically to aureomycin In one a perirectal infection led to cellulitis and arthritis on hospitalization gas was demonstrated in the infected areas Only Bacteroides funduliformis was isolated and it can form gas In 13 patients the infection originated in the female genital tract Six were critically ill and nine showed persistent septic fever Two died The most ill defined and clinically insignificant group was the seven patients with urinary tract infection No systemic *involvement*

(6) A I t M d 36 56 76 J y 195

drugs require either fasting or restricted diets and purges before, with or after therapy Oil of chenopodium is best tolerated when the patient is at rest in bed

On the basis of reports by other workers the authors began to treat ascariasis with hetrazan® in Haiti in March 1950 Twenty six patients were given 6 mg./kg body weight three times daily for five days In an attempt to shorten the course of therapy 14 others were given 10 mg/kg three times daily for three days Evidences of toxicity developed in this group

To simplify administration of hetrazan® especially to children a palatable cherry flavored sirup containing 30 mg/ml was prepared Three groups of patients were selected for treatment In the first group of 43 sirup of hetrazan® in doses containing 13 mg/kg was administered once daily for three successive days In the second group of 24 patients a dose containing 13 mg/kg was administered the first day and 20 mg/kg once daily on the second and third days In the third group 37 patients were given doses of sirup of hetrazan® containing 13 mg/kg once daily for four successive days

Under semifield conditions it was impossible to count the actual number of worms expelled The authors learned from the patients who are well acquainted with the appearance of ascaris that expulsion of the worms began on the second day of treatment the largest numbers were expelled on the third and fourth days after treatment was started with either sirup or tablets Worms that were examined were stunned dying or dead some of the dead worms appeared to be partly disintegrated

Sirup of hetrazan® because of its excellent anthelmintic efficiency (91 94% of the ascaris removed) low toxicity (less than 1%) and ease of administration is the agent of choice for treatment of human ascariasis and should be useful for mass treatment in eradication campaigns

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MISCELLANEOUS INFECTIOUS DISEASES

Bacteroides Infections are being grossly neglected mainly because most physicians are not familiar with this gram

responsible for infections of these organs and permitted ready implantation of highly antibiotic and sulfonamide resistant chromobacterium It is evident that the ever widening use of antimicrobial agents will be associated with the discovery of disease caused by a wide variety of unusual micro organisms

[The possibility that apparent increase of this kind of infection may be a secondary result of antibiotic therapy is intriguing —Ed]

Erysipeloid of Rosenbach Review of 30 Cases J A MacDougall[8] (St Thomas s Hosp London) is mainly con cerned in this report with assessing the value of penicillin therapy in this condition According to Klander in 1948 the Erysipelothrix rhusiopathiae gives rise to three forms of in fection in man (1) mild localized cutaneous infection (2) diffuse or generalized cutaneous eruption with constitutional symptoms and (3) a septicemic form All 30 cases fell in the first group the type of lesion first described as erythema serpens (1873) Rosenbach in 1884 isolated the organism and reproduced the disease experimentally The bacillus is a slender rod 1 1 5 μ wide and 2-4 μ long nonmotile and non sporing It is widely distributed in nature wherever nitroge nous compounds are decomposing it has been recovered from slime of fish and from houseflies and horseflesh In human infections it can be cultured by ordinary laboratory methods from skin removed from the advancing edge of the lesion

Diagnosis in all cases was made clinically Biopsy was not considered justifiable because surgery is never required in treatment History of trivial injury while handling meat fish or other forms of food was given by 18 patients In cubation period averaged two to three days 16 patients did not request treatment until over a week after the first ap pearance of the lesion The infected area was always the hand or fingers there was superficial itching or smarting with a feeling of tightness and stiffness of the underlying joints The throbbing pain of a pyogenic infection was not present The lesion was an erythematous patch spreading from the site of inoculation varying in color from pink to deep purple with a fairly distinct raised margin and hot but not acutely tender Three patients had fever and malaise and one vomited Local disability was not great All were treated as outpatients

(8) La t 1 1345 1346 J 23 1951

was noted Cutaneous infection was noted in one patient and had a mild course Two Negro male infants had middle ear infections They were critically ill and subsequently had septicemia One died and one recovered after a prolonged illness

Streptomycin sulfadiazine penicillin and aureomycin were used Aureomycin was by far the most effective A proper therapeutic regimen in bacteroides infections should include adequate aureomycin dosage maintenance of nutrition and of proper electrolyte balance by appropriate intravenous use of fluids and whole blood and surgical procedures indicated for drainage of purulent material

Infection Due to Chromobacteria Report of 11 Cases Though rare in human beings 11 such infections were observed by Richard P Wheat Anne Zuckerman and Lowell A Rantz[7] (San Francisco) One patient died of bacterial endocarditis Chromobacteria are nonsporulating aerobic bacilli usually motile and gram negative producing yellow red or violet pigment which is generally insoluble in water The chief member of the group producing violet pigment is violaceum that of the group producing pink or red pigment is Chromobacterium prodigiosum and that of the group producing yellow or orange pigment aquatilis The infection was recognized and organism first recovered in the authors patients after some type of urinary tract manipulation including catheterization cystoscopy and genitourinary surgical treatment These procedures did not take place in the same clinic and different operators were involved as well as various methods of sterilization of instruments An epidemiologic study failed to locate the source of this unusual organism In all patients the organism was present in the urine in large numbers In two patients it was recovered from the blood bacteremia was transient in one and led to fatal endocarditis in the other

It is not surprising that so many patients with urinary infection by this unusual organism were observed since the obstructed and instrumental urinary passages are fertile soil for multiplication of bacteria not commonly the cause of disease elsewhere Use of multiple antibiotics was a contributing factor as they eliminated all the usual organisms

(7) A M A A h. Int Med 88 461 466 Octobe 1951

coccus) and the anaerobic which include cocci (especially nonhemolytic streptococcus) and the bacteroides group (especially B melaninogenicus) Except for E coli all are weak producers of gas E coli rapidly ferments sugar to produce lactic acid carbon dioxide and hydrogen The fermentation process is aided by anaerobic conditions and abetted by the other organisms which act synergistically with it

Since the combination of infection high sugar content in tissue and impaired circulation is so common it is strange that the condition is not described more often it may be due to the fact that E coli is only rarely the cause of suppurative inflammation in the extremities

In nonclostridial gas infections treatment consists of multiple incisions and administration of antibiotics Prognosis is excellent provided the disorder is recognized and adequately treated

Nephropathia Epidemica a New Infectious Disease in Northern Scandinavia In 1933 and 1934 Gustaf Myhrman[1] observed *seven cases characterized by acute onset without* preceding disease of chills fever and headache pronounced proteinuria of short duration scanty urine sediment hyposthenuria slightly decreased glomerular filtration and elevated nonprotein nitrogen Blood pressure was not increased All patients recovered in a short time During the last few years Myhrman has observed about 30 cases in Boden Sweden Many colleagues in that part of the country have observed similar cases but none has been reported in the English literature

No etiologic agent has been found although examinations were made for spirochetes and human transmission was attempted Many cases have been reported in lumbermen and others living under poor hygienic conditions usually in contact with mice which Myhrman believes are vectors

Soon after the acute onset the patient complains of abdominal pain Fever subsides in a few days and renal involvement is noted Proteinuria up to 6 per cent characteristically disappears in 9 13 days Urine output is low at first but soon amounts of 3-4 L daily are excreted always with hyposthenuria Only a few red cells white cells and casts are found Nonprotein nitrogen may rise to 180 mg per cent

(1) A ta m d d 140 5 56 1951

"None received local application but a patient so desiring was given a sling to rest the arm Aqueous penicillin 200 000 or 500 000 units once or twice a day was administered to 28 patients in 2 who refused penicillin and were untreated the lesions resolved spontaneously in 10 days in 1 and 14 in the other Erysipeloid is a self limiting disease lasting an average of three weeks there is, however considerable variation Recurrence is said to be common both in patients in whom the lesions resolve spontaneously and in those treated with penicillin The present cases show that no definite amount of penicillin will prevent recurrence However desquamation was noted at the site of the lesion if penicillin had been given and not otherwise and desquamation once having appeared did not recur For this reason eight patients were given 200 000 or 500 000 units of aqueous penicillin injections twice daily until desquamation took place (three to five days) None of these patients relapsed Treatment for shorter periods was followed by some relapses

Nonclostridial Gas Infection in the Diabetic Review of Literature and Report of Three Cases Maxwell Spring and Sidney Kahn[9] (Bronx Hosp New York City) note that although gas gangrene the infection produced by Clostridium perfringens (Bacillus welchii) is familiar to many it is not well recognized that other organisms such as Escherichia coli and anaerobic streptococcus can also produce gas infection in tissues This unusual condition is generally confused with gas gangrene its early differentiation from that disorder yields a different problem in therapy and prognosis

Formerly it was believed that crepitus in infected tissue indicated gas gangrene When it was found in a leg amputation was done as a lifesaving procedure to prevent spread of infection especially when arteriosclerosis obliterans was present However when there is an adequate culture medium as is found in the high dextrose content of the tissues of the diabetic patient other organisms are capable of producing gas in tissues In addition gas may accumulate because circulation in the diabetic limb is too poor to carry it away The nonclostridial organisms that produce gas infection may be the aerobic which include coliform bacilli (especially E coli) and pyogenic cocci (especially nonhemolytic strepto

(9) A M A Arch Int Med 88 373 377 September 1951

weeks elapsing before complete recovery and loss of frequency of micturition which is probably the most persistent symptom During the acute stage the leukocyte count is considerably raised up to 50 000 cells/cu mm and shows a shift to the left Blood nonprotein nitrogen level is often raised to 100 mg./100 cc Albuminuria hematuria and cylindruria are common Urine specific gravity is 1 005 1 010 No specific treatment has been evolved All antibiotics have been used without benefit Mortality rate is about 12 14%

[This dramatic new disease deserves careful investigation Claims have been made that it is due to a virus but the clinical picture is more suggestive of rickettsial or leptospiral infection —Ed]

Acute Nonspecific Pericarditis E Wayne Gilley (Cincinnati) Malcolm C McCord and James T Taguchi[3] (V A Hosp Dayton O) report nine cases of this essentially benign disease which often presents many features closely resembling those of myocardial infarction In the past decade there has been increased awareness of this form of pericarditis of unknown etiology and attention has been directed toward its frequent confusion with coronary thrombosis

Acute nonspecific pericarditis is generally considered to be inflammatory and of infectious origin The latter view is supported by the high incidence of recent antecedent or associated respiratory infections In seven of the nine patients respiratory infection was a prominent feature Pain is an outstanding symptom also and may cause some initial confusion with coronary artery thrombosis The chest pain is very much like that of myocardial infarction except for its relation to respiration A pericardial friction rub may be heard in both types of disease although there appear to be differences which are of distinct value in establishing the correct diagnosis The pericardial friction rubs associated with nonspecific pericarditis are present earlier more intense more constant and heard over a wider area than those of myocardial infarction Therefore presence of a friction rub at the time of initial pain is an important point in favor of nonspecific pericarditis In six patients a loud pericardial friction rub was heard over a wide area of the precordium The friction rub of myocardial infarction is usually transient and localized

Characteristic ECG changes of nonspecific pericarditis are

(3) Am. J M S 222 249 2 6 Septemb 1951

reaching its highest level when the patient begins to feel better There are no changes in the blood smear In 11 of 16 cases in which thymol turbidity tests were done results were positive In only one case was the liver palpable Icterus and splenomegaly were never noted Latent edema indicated by subsequent weight loss was occasionally evident

Acute Epidemic Hemorrhagic Fever is discussed by Donald D Beard (M C Royal Australian Army) This is a disabling little known fever which has been noted among troops in Korea Japanese investigators first recognized epidemics of this illness among troops stationed in Manchuria as early as 1935 They have established a filtrable virus as the cause The condition has no immunologic relation to any other virus disease It is probably transmitted to man and probably to horses by the mite Laelaps jettmari vitzhum the host for which is the field mouse Apondemus agrarius

The outstanding pathologic feature is pronounced disturbance of the peripheral circulation with paralysis of the capillaries causing stasis and transudation and later spread to larger vessels This becomes apparent in the skin and visible mucosa and autopsy has shown that many organs are affected The hemorrhagic tendency differs in extent from case to case

After an incubation period of 14 21 days a short prodromal stage begins which includes malaise anorexia nausea and pain in the extremities Then the temperature rises rapidly in two or three days to 103 105 F where it remains for three to five days it then falls quickly to normal or subnormal usually by rapid lysis During the acute stage while the temperature is elevated the following signs and symptoms are present severe headache hiccup epigastric pain vomiting sore eyes with blurred vision mild dyspnea myalgia low backache and the signs of capillary disturbance—petechiae of the skin particularly of the face and the upper part of the trunk gingival hemorrhage epistaxis melena and hematuria There is a peculiar odor about the patient and the tongue has a dry yellow coating Oliguria is present from the start Within two to five days of the fall in temperature most patients begin to improve good signs being diuresis and appetite Convalescence may be lengthy up to four to six

(2) M J A (at 1 94 293 M 1 195

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(3) Am. J M S 22 249 256 September 1951

not found in all patients especially during the initial period of illness when early diagnosis is desired On hospitalization or shortly thereafter ECG s showed no significant abnor malities in five patients In three elevation of the S-T seg ments was significant primarily in comparison with subsequent tracings demonstrating a return to normal Inverted T waves were present on admission in two patients but these changes were of little value in making an early specific diagnos It was notable that in two patients paroxysmal supraventricular tachycardia developed during hospitalization apparently thi is not uncommon Fever characteristically heralded onset of illness and was often present with the initial pains in con trast with the usual later occurrence of fever in myocardial infarctions Leukocyte count varied from normal to 14 000/cu mm with differential of the higher counts showing the poly morphonuclear percentage to be increased In two thirds of the patients cardiac silhouette was increased in size and roentgenologic follow up study demonstrated in mo t patients a rapid return to normal Such degrees of cardiac enlarge ment are unusual in acute myocardial infarction and the subsequent rapid change in heart size favors pericardial effusion When aspirations have been done the fluid has been described as serohemorrhagic This raises the question as to whether anticoagulant therapy might not be contraindicated which further emphasizes the need for differentiation of this condition from myocardial infarction

(Here is a condition we should all become familiar with An erroneous diagnosis of myocardial infarction is likely to do much harm in terms of anxiety change of activity etc —Ed]

Recurrent Uveitis (Behçet's Syndrome) and Encephalo myelomeningitis Behçet s syndrome is characterized by re current uveoretinitis aphthous stomatitis genital ulcers often combined with skin eruptions of various types B F Silfver skiold[4] (Stockholm) describes three cases of recurrent uveo retinitis with pronounced visual impairment on which were later superimposed recurrent severe attacks of spastic paresis in the limbs especially in the legs In two cranial motor nerves were involved Genital ulcerations and aphthous stomatitis occurred in two and a skin eruption in one During the periods of exacerbation the temperature was raised

(4) Acta p ych at et eu ol 26 443 453 1951

sedimentation rate increased and cerebrospinal fluid showed pronounced pleocytosis One patient died Autopsy revealed encephalomyelitis with softened and necrotic areas in the peduncles the bulb and the upper part of the spinal cord Previous reports have linked central nervous system dis orders with this syndrome but the neurologic pictures were not so uniform as noted here

[This syndrome (pronounced beh shet) resemble the Stevens John son syndrome both may be expressions of the same sort of proces not necessarily infectious in nature —Ed]

COLLAGEN DISEASES

Present State of Knowledge Concerning Pathogenesis and Treatment of Rheumatic Fever is discussed by Maclyn Mc Carty[5] (Rockefeller Inst) According to the concept of patho genesis most widely held at present the initial event is a hemolytic streptococcic infection of the upper respiratory tract This in turn initiates a series of events involving the action of streptococcic products and the complex host reaction thereto leading ultimately to the manifest disease which may occur and be perpetuated in the absence of demonstrable bac teria The interactions between host and parasite are thought to involve antigen antibody mechanisms Some question has been raised as to whether rheumatic fever is invariably pre ceded by a streptococcic infection The burden of proof rests on those who wish to incriminate other agents When there is no apparent preinfection by streptococci recrudescence of activity rather than a true recurrence must be excluded In recrudescence many stimuli can cause a flare up of rheu matic activity McCarty holds to the specificity of the strepto coccus The pattern of antistreptolysin O response in a random group of rheumatic fever patients is essentially identical to that in patients in whom the disease develops during an epi demic of known streptococcic infection

More extracellular products characterized as toxins or enzymes have been isolated from group A streptococci than from any other organism This is probably a result of the more intensive study of streptococci Many of these prod

(5) B N w Y k A d M d 8 307 3 0 M y 195

ucts are of unusual interest Streptokinase has been implicated as a possible factor in the sequelae of streptococcic infections This enzyme has the property of activating plasminogen the precursor of a proteolytic enzyme present in mammalian serum especially human Streptolysin O in addition to its hemolytic action on mammalian red cells has a toxic effect on isolated frog s heart Hyaluronidase owing to its action on one of the main constituents of the ground substance immediately becomes suspect in rheumatic fever a disease which seems to affect connective tissue In addition to these extracellular substances the streptococcus cell itself possesses an undetermined number of constituents among which there may be one or more of special importance in the induction of delayed effects of streptococcic infection Thus although there is no proof of the relation of streptococci to rheumatic fever there is no lack of potential agents in the streptococci for initiation of the pathologic processes

Several of these products have been shown to produce individually specific antibody responses following natural infections This assumes significance in the light of the concept that antibody antigen mechanisms are involved in the pathogenesis of rheumatic fever Among the evidences cited in support of this concept are the following the latent period between the original infection and onset of rheumatic fever coincides roughly with the period required for the appearance of large amounts of circulating antibody in addition patients who develop rheumatic fever have on the average a quantitatively greater antibody response to the various streptococcic antigens than patients who do not It has also been shown that rheumatic fever lesions can be simulated in animals by certain technics of in vivo antigen antibody reactions

Largely on the basis of nonspecific staining reactions the fibrinoid material observed in rheumatic fever lesions has been considered to represent altered or degenerated colloid Because of this the view was advanced that the protein collagen was the initial site of injury and rheumatic fever was classified as one of the collagen diseases Recent studies indicate that these assumptions are not tenable and that the fibrinoid material is probably not derived from collagen At present the problem of the initial site of injury cannot be considered settled Proponents of the streptococcic theory of

etiology find it difficult to explain the persistence of rheu matic activity in the absence of demonstrable bacteria

Problems also exist with regard to therapy There are still differences of opinions concerning the value of salicylates No one has been able to establish what effect they have on development of permanent cardiac malformations Both sali cylates and the hormones now used in the treatment of rheu matic fever are thought to achieve their effect by interfering with the host reaction to the antigenic agents without affect ing the underlying process itself This is suggested by the rapid return of symptoms on cessation of such therapy How ever this does not eliminate the possibility that the interfer ence might have a retarding influence on the ultimate develop ment of the lesions

Although the fields of pathogenesis and therapy are yet in a state of flux many of the past advances have been con solidated in recent years and co ordination and synthesis of new information based on new facts will probably lead more closely to the truth

[An excellen and authoritative discussion Those specially interested should read the original article —Ed]

Acute Rheumatic Fever in the Young Adult White Male is analyzed by James G Hirsch and David M Flett[6] (Chey enne Wyo) Relatively little information on the natural his tory of active rheumatic fever in young adult white males is available For two years 109 members of the Air Force were observed throughout the course of their illness 92% were 17 21 years old When hospitalized for rheumatism 24% gave a history of rheumatic fever or chorea and 78% could recall significant upper respiratory infection 6-40 days before onset of rheumatic symptoms with a mean interval of 19 days Re spiratory complaints varied but most commonly consisted of sore throat for three to four days coupled with fever and malaise

The most consistent and prominent complaint was joint pain Anorexia weakness weight loss myalgia fatigability and malaise were other common but less specific symptoms Complaints referable to the cardiovascular system were rare Objective changes with local heat erythema or swelling around one or more joints were noted in 91% of the patients

(6) Am J M S 2 1 599 611 J 1951

producing severe and incapacitating discomfort Initial arthritis was commonly localized in a large weight bearing joint such as the knee or ankle

Although 90 of the 109 patients had no murmur by the end of the observation period (average 8 months) many of them may later Although diastolic murmurs are said to be rarely of functional origin many apical diastolic murmurs were transiently perceptible in the acute stage Distinct cardiac enlargement apparent on teleoroentgenograms occurred in 12 patients whereas only 2 instances of decompensation both mild were found Pericarditis was manifested by audible friction rub in 14 patients

Skin lesions accompanying acute rheumatic fever are many and variably specific Five instances of erythema marginatum were encountered in this series and one of erythema multiforme at the time of hospitalization No instances of subcutaneous nodules were encountered despite daily scrutiny of each patient

No chorea occurred during hospitalization and pneumonitis attributable only to rheumatism was found in eight patients In two peritonitis symptoms were prominent features of acute rheumatism On the whole the course was benign One patient resumed moderate activity after only nine weeks In the most protracted instance the patient was not allowed up for 62 weeks The mean time before a patient was up was 21 weeks

Laboratory findings disclosed mild leukocytosis (12 000 15 000) in most patients Antistreptolysin O titers were performed by a modification of the method of Hodge and Swift Considering any titer over 150 units elevated the antistreptolysin level was elevated in all but one patient During the respiratory infection phase which preceded rheumatism 32 of 38 patients had positive throat cultures for group A streptococci and evidence of recent streptococcic infection was discernible in nearly every patient in many instances evidence suggested multiple streptococcic infections

Aspirin therapy was given to 60 patients and withheld from 44 Results indicate that aspirin may have had some effect as shown by slight reduction in mean duration of fever and arthritis Sedimentation rate returned to normal more rapidly in those given aspirin although salicylates have

been known to reduce sedimentation rate per se Incidence of heart murmurs indicative of valvular damage did not differ statistically in the two groups

Electrocardiograms if taken daily could demonstrate

SIGNIFICANT ELECTROCARDIOGRAPHIC ABNORMALITIES OBSERVED IN 93 CASES

T	%
Atrioventricular dissociation	12
First degree heart block	43
T wave inversion leads I and CF	16
S T segment elevation and T wave inversion	3
First degree heart block plus T wave inversion	26

carditis in a high percentage of patients a type distribution of significant abnormalities is given in the table

Prevention of Rheumatic Fever [7] A controlled study was made on a total of 2 360 Army personnel of whom 1 178 patients received penicillin and 1 162 controls had no specific treatment Procaine penicillin G suspended in peanut oil containing 2% aluminum monostearate was given intramuscularly as soon after admission as possible Rigid criteria for diagnosis were followed using a modification of the Jones classification Major criteria included carditis migrating polyarthritis history of recurrences chorea and subcutaneous nodules minor manifestations included fever arthralgia skin rash nonspecific electrocardiographic changes and elevated sedimentation rate Diagnosis of definite acute rheumatic fever required two major or one major and two minor manifestations

Acute rheumatic fever developed in only two of those given penicillin and in 28 controls Despite variation in the carrier rates penicillin therapy effected a reduction of group A streptococci when compared to the controls There was a definite relation between effectiveness of such treatment and the penicillin dosage schedule For antibody suppression three injections totaling 1 200 000 units of depot penicillin were twice as effective as a single injection of 600 000 units

Results indicate that penicillin therapy for acute streptococcic infections almost completely prevents subsequent occurrence of rheumatic fever and emphasize the close relation between the two If the incidence of rheumatic fever is to be reduced materially by early penicillin therapy streptococcic infections must be diagnosed accurately and early In such

(7) U S Armed F M J 2 607 613 Ap 1 19 1

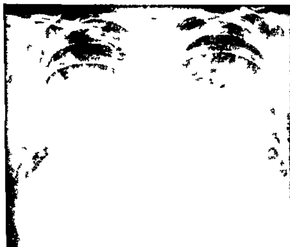
illnesses there are sudden onset of sore throat difficulty in swallowing fever redness and edema of the soft palate tonsils and oropharynx, discrete or confluent exudate large tender cervical lymph nodes and in some elevated leukocyte count In areas where streptococcic infections are epidemic exudative tonsillitis or pharyngitis should be considered of streptococcic origin

[This is most convincing evidence of the likelihood that rheumatic fever can be reduced by prompt and adequate therapy of the initial streptococcic infection —Ed]

Roentgenologic and Pathologic Observations in Antigenic Pneumonitis Its Relation to Collagen Diseases Derangement of the intercellular collagenous substance may be an important common factor in development of the collagen diseases The disorders most commonly considered collagen diseases are hypersensitive states which result in sensitization reactions to foreign protein drug sensitization blood incompatibility in transfusions acute glomerulonephritis periarteritis nodosa rheumatic pneumonitis rheumatoid arthritis disseminated lupus erythematosus dermatomyositis and scleroderma These widely differing diseases seem to have little to identify them with a common etiology but since signs and symptoms are often similar a common causative factor must be considered In all there is an associated common fundamental pathologic lung reaction Utilizing the lungs as a roentgen window for observation of any pathologic process which might be going on in the body L R Sante and J P Wyatt[9] (St Louis Univ) attempted to throw some light on the nature of these diseases by correlation of roentgen and histologic observations

Roentgenologically the collagen diseases seem to be divided into two major groups There are those in which there is an acute antigenic response associated with glomerulonephritis and antigenic (azotemic) pulmonary edema The hilar regions and inner zones of the lungs present dense blotchy areas of increased density like those seen in pulmonary edema which radiate out toward the periphery but stop short of the outer edges of the lungs leaving clear peripheral zones The picture differs from that of acute pulmonary edema due to cardiac failure in that it stops abruptly before reaching the outer lung margins and is not associated

(9) Am. J Roentgenol 66 527 545 October 1951





F g 5 (top) —P t t od sa w th my t d t g (t m) pulmo-y dem L g t on g d ally b d d b t d t p t d C firmed by m 1 b op

F g 6 (bottom) —Th w k 1 t A t g p lm y d m t compl t ly d

(Courte y f S t L R d Wy tt J P Am J Roe tg 1 66 527 545 O tob 1951)

with an enlarged cardiac shadow Ordinary congestion and edema of the lungs due to cardiac failure fill the entire lung structures especially in their bases Sensitization reactions to foreign protein drug sensitization blood incompatibility in transfusions acute glomerulonephritis and periarteritis nodosa (Figs 5 and 6) belong to this group The rest of the collagen diseases belong to the second group in which there is no indication of lung reaction up to the terminal stages At this time pulmonary edema may be seen it is never of the azotemic type but rather irregular collagenous deposits throughout the lung field

The mere fact of common connective tissue involvement in all of these diseases does not preclude the possibility of several causative agents with consequent variation in tissue response However roentgen examination of the chest should aid differentiation of the two groups

[Proper evaluation of lesions such as those described here can be of great help in difficult clinical problems —Ed]

Use of Cortisone in Erythema Nodosum is reported by Stanley Farber and Harry Mandelbaum[1] (Jewish Hosp of Brooklyn) Clinical manifestations of the disease are probably the reactions of a sensitized person to a wide variety of sensitizing or antigenic substances—bacterial toxic or chemical

Woman 25 three months previously had noted onset of purple and red areas on the legs first on the flexor and then on the extensor surfaces They were accompanied by drawing pains in the legs Various agents were without effect On hospitalization extensor surfaces of both legs showed discrete and coalescing pink macular and maculopapular nodules 1 3 cm in diameter extending up to the anterior portions of the thighs They were slightly tender Clinical diagnosis was erythema nodosum Biopsy of skin from a lesion showed no change in the epidermis Cutis and panniculus had the typical appearance of erythema nodosum Treatment was started with 5 3 Gm sodium salicylate daily thiamine hydrochloride and ascorbic acid with no regression of the lesions after a week New lesions continued to appear on the legs and arms Para amino benzoic acid was added Since no improvement was noted the medications were discontinued Cortisone 300 mg was given intramuscularly The next day the lesions were fading and tenderness was gone 200 mg cortisone was given The following day the lesions had disappeared After administration of another 200 mg cortisone therapy was discontinued Three days later biopsy of skin from

(1) A.M.A. Arch Int. Med. 88 395 399 Sept mbe 1951

an area adjacent to the site of removal of the first biop y specimen and previou ly demarcated as an area of erythema nodosum howed normal skin and subcutaneous tissue The manifestations of erythema nodosum did not recur

Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber Christian Disease) Review of Literature and Report of Case This disease is characterized by recurrent episodes of fever and formation of single to multiple crops of tender or painless freely movable inflammatory and necrotic nodules in the panniculus adiposus The nodules are nonsuppurative and occur most commonly on the legs abdomen breasts and arms They range from 0 5 to 3 cm in diameter The overlying skin may be normal but usually is red or violaceous and may be warmer than normal Although only about 50 cases have been reported John D Hallahan (Media Pa) and Thomas Klein (Philadelphia) believe the disease often goes undiagnosed because of its usually benign nature and unfamiliarity with the entity Most cases occur between ages 20 and 40 but have been seen in all age groups Females are affected three times more often than males

Histologically the interstices of the adipose tissue are more or less heavily infiltrated with leukocytes of various types with separation and partial to complete resorption of fat cells serous atrophy and even necrosis of fat have been observed Lipophagocytosis by macrophages is sometimes prominent The reacting leukocytes comprise lymphocytes plasmacytes cells of the monocyte macrophage series and a sparse interspersion of neutrophils and eosinophils Multinucleated giant cells are occasionally encountered There is also proliferation of local fibroblasts and reticulum cells The inflammatory process is singularly limited to the fat lobules proper intervening fibrous septa and trabeculae being spared

Onset is insidious and without prodromes The patient simply notices the appearance of the lesions somewhere on the body Their development may be heralded by chills nausea malaise and fever as high as 104 F Muscle pains and regional adenopathy can occur The nodules may remain from several days to months finally regressing and leaving dimples in the skin or disappearing without any superficial trace Recurrences with the same clinical findings occur at intervals

(2) A I t M d 34 1179 1 01 M y 1951

of a few days weeks months or years The patient may be so ill during a relapse as to need hospitalization or be comfortable and capable of carrying on his daily work without interruption Between relapses the only evidence or residuum of the disease may be the dimpled skin representing fibrotic intervals in the fatty tissue which had previously undergone inflammatory changes

This disease must be differentiated particularly from lipomatosis adiposis dolorosa erythema nodosum erythema induratum and dermatomyositis Diagnosis is based on the clinical picture and a biopsy of the involved fat Prognosis is guarded Several cases have been reported in which the patient apparently died of the disease Most patients live with the threat of recurrence of symptoms There is no specific treatment

[The clinical picture is not as difficult to remember as the name! *Classification of this condition under the heading collagen diseases* may not be justified —Ed]

Temporal Arteritis with Blood Culture Positive for Streptococcus Favorable Action of Aureomycin Temporal arteritis is only a localized manifestation of a highly diffused vascular disease according to Y Boquien J P Kerneis D Hervouet and Moyon[3] (Nantes) They report a case in which aureomycin therapy brought about an apparent cure followed later by a relapse

Man 78 had fever and frontal headache Illness began four months before with fatigue and cough Severe intermittent headaches appeared localized in the left temporofrontal region and occurring chiefly in the morning accompanied later by chills Symptomatic treatment brought no relief Finally he had a severe chill lasting several hours with fever and transitory confusion and *simultaneously violent pain in the head spreading to the neck* on the left side A blood culture taken immediately after the chill was negative Several similar attacks occurred On hospitalization the dominant symptoms were headache chills and fever Headaches were characterized by cervical as well as cranial pain beginning at the left supraclavicular hollow progressing along the carotid and temporal vessels and attaining maximal severity in front of the ear and at the external part of the frontal bone Similar but less severe pains were felt on the right Pain was constant and constrictive during paroxysms pain became intolerable assuming a pulsating character diffused through the posterior part of the skull

(3) Pr se med 59 1774 1776 Dec 25 1951

Paroxysms were preceded by chills lasting a half hour and accom panied by profuse sweats Pain was greatly increased when the patient lay on his left side Temperature oscillated from 99 to 102.2 F falling during the night and rising again about 6 a m

On examination the temporal arteries were prominent espe cially on the left (Fig 7) The left artery was pulsating and hard and there were nodules throughout its length Some periarterial swelling was present palpation was exquisitely painful The same characteristics were present to a lesser extent on the right except that pulsation of the artery may have been slightly stronger Ex ploration of the arterial system showed a greater intensity of pulsa



F g 7 —T mpor l t ry th ck ed ou d q t p m (C t y f Boq Y t al P se med 59 1774 1776 Dec. 25 1951)

tion at the level of the right carotid and axillary arteries The venous system was not affected Ocular symptoms seemed due to senile opacities in the crystalline lens there was no photophobia or pain from pressure on the eyeballs Fundus examination dis closed a slight left macular edema without signs of arteritis some days later the left eye suddenly became blind as a result of papil lary edema Blood culture revealed a gram positive coccus highly resistant to both penicillin and streptomycin At operation the superficial temporal artery was resected under local anesthesia The pain then decreased and ceased to be paroxysmal chills were less severe but persisted temperature did not seem to be affected Peni cillin was given and pain and chills virtually disappeared The left eye remained blind however and fever continued Penicillin was stopped (total dose 7 000 000 units in seven days) and aureomycin treatment begun The general condition improved asthenia dimin ished and appetite returned Pain and chills disappeared com pletely and sleep became possible Temperature no longer showed

peaks above 100 4 F Total dose of aureomycin was 27 Gm given in nine days A week later the patient was discharged greatly improved

In this case the headache an essential symptom of the disease was not entirely characteristic the pain being widely diffused and localized more in the neck than in the head Aureomycin reduced the fever and improvement in the general condition led to a hope that the patient was cured His death some months after leaving the hospital however again shows the extreme seriousness of temporal arteritis

[The one positive blood culture is of doubtful significance Benefit from aureomycin therapy has also been reported from England (see the 1951 YEAR BOOK OF MEDICINE p 118) —Ed]

DISORDERS SIMULATING INFECTIOUS DISEASES

Polymer Fume Fever Polymerization of chemically active tetrafluorethylene produces an inert powder which is affected only by molten alkali metals below its melting point Polytetrafluorethylene (teflon fluon) is remarkably thermostable resisting temperatures up to *327 C* at which it becomes a rubbery translucent mass At *360 C* and more so with rising temperatures it gives off an invisible fume which produces toxic symptoms if inhaled

According to D Kenwin Harris[4] mild symptoms suggesting coryza appear after a latent period of a few hours First there is discomfort in the chest especially on taking a deep breath then a gradual increase in pulse and temperature and perhaps in the respiratory rate followed usually by a chill and sweating Physical examination generally gives negative results however a few rales may be found in the more severe cases There is an early mild leukocytosis The acute attack lasts but a day or two and recovery is complete Because of the mild course medical attention may not be sought unless the attacks recur

These signs and symptoms closely resemble those of metal fume fever or brass founders ague produced by inhalation of metal fumes notably zinc cadmium copper iron nickel and lead Other investigators believe that the cause of this

(4) Lancet 2 1008 1011 Dec 1 1951

illness is an extremely fine sublimate liberated from the polymer and carrying absorbed hydrofluoric acid From preliminary experiments Harris concluded that at temperatures exceeding about 150 C fluon liberates a mineral acid whose concentration becomes greater as the temperature rises until at about 300 C the products become dangerous to life producing severe and widespread irritation of the lungs with hemorrhage and edema The acid and the sublimate have not been identified

[As mentioned in the article this syndrome has been encountered following inhalation of other fumes Pathogenesis of the chill and fever is mysterious —Ed]

Brain Tumors Simulating Meningitis Patients with symptoms of meningitis are often successfully treated with chemotherapeutic agents but because many causes of meningeal irritation encountered are not of infectious origin caution must be taken with such a therapeutic procedure Failure of the patient to respond adequately to the therapy may indicate atypical cause and need for further investigation Ian A Brown and William T Peyton (Univ of Minnesota) report three cases to emphasize these facts

CASE 1 —Man 27 had a dermoid cyst involving inferior portions of both frontal lobes there was a long history of sinusitis Blowing of the nose was followed by onset of severe meningeal reaction fever leukocytosis and cerebrospinal fluid pleocytosis Cerebrospinal fluid studies showed pressure 26 mm Hg and 1 744 white blood cells/cu mm 97% polymorphonuclear and 3% mononuclear Intracranial pressure was increased after encephalography Recovery followed partial removal and evacuation of an intracerebral cyst

In this case a large dermoid cyst of the frontal lobes simulated meningitis It is well known that the contents of dermoid and epidermoid cysts of the brain are irritating to the ependymal lining

CASE 2 —Woman 69 was semicomatose with signs suggesting meningitis There were 13 400 leukocytes 85% polymorphonuclear Cerebrospinal fluid showed 122 white blood cells 73% polymorphonuclear three days later there were 560 white cells 96% polymorphonuclear Abnormal course and failure to respond to antibiotics prompted further investigation which revealed brain tumor of frontal lobes diagnosis was glioblastoma multiforme Meningeal reaction was thought due to both tumor necrosis and products of hemoglobin breakdown

(5) J N g 8 459 468 Sept mb 1951

CASE 3—Man 23 had clinical and laboratory signs of meningitis White blood cell count was 17 000 with 81% polymorphonuclears and 19% lymphocytes Cerebrospinal fluid showed pressure 400 mm water 694 white blood cells 89% polymorphonuclears and 11% lymphocytes Antibiotic therapy was begun Bilateral choked disks developed with retinal hemorrhages ventriculography showed bilateral symmetrical hydrocephalus Two days later he suddenly died Presumptive diagnosis was tumor of the third ventricle autopsy confirmed it as cerebral varix

Numerous agents may cause meningeal irritation and meningitis Acute demyelinating diseases may elicit intense lymphocytic polymorphonuclear and plasma cell reactions attributed to disintegration products of nerve tissue Bender injected lipoid fractions derived from myelin into the subarachnoid space and obtained a polymorphonuclear response in the cerebrospinal fluid Cholesterol was more potent than cerebrosides in activating such a response It is also known *that cerebrospinal fluid may contain large numbers of poly*morphonuclear cells after operations on cholesteatomas or cholesterol containing cysts of the brain Rapid disintegration of myelin due to embolism or thrombosis of a vessel is followed by a polymorphonuclear response in the meninges Jackson has shown that bilirubin is probably the specific agent in the blood responsible for the meningeal reaction Cerebral tumors as a rule produce no change in cell count of the cerebrospinal fluid When intracranial tumor is associated with numerous cells in the cerebrospinal fluid necrosis of the tumor or myelin destruction in the perineoplastic area is presumed to be the cause Of 43 patients with glioblastoma multiforme 13 had pleocytosis with a range of 14 70 cells many of which were polymorphonuclear

[I once saw a child with brain tumor given a course of streptomycin therapy based on an erroneous diagnosis of tuberculous meningitis —Ed]

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SARCOIDOSIS

Isolation of Virus in Some Cases of Boeck's Sarcoid is reported by Sven Lofgren and H Lundback[6] (Stockholm) In 14 of 64 patients with a weak tuberculin reaction and bilateral enlargement of hilar nodes diagnosis of sarcoidosis was established by biopsy Similar observations were later

(6) Wien klin Wchnschr 63 398 401 J 1 1951

made in 150 cases Therefore presence of a weak tuberculin reaction and bilateral enlargement of hilar nodes is considered the first stage of pulmonary sarcoidosis

Material obtained by gastric lavage two cutaneous infiltrations and a lymph node from three patients with chronic pulmonary sarcoidosis five with bilateral hilar lymphomas and two with cutaneous sarcoidosis were examined for presence of a virus Material was grown in eggs and presence of virus judged on the basis of results of agglutination and precipitation tests

In seven cases a virus was found It was almost identical with mumps virus on which work was being carried out simultaneously in the laboratory No virus could be isolated from four gastric washings from normal persons working in the laboratory However it was found in three of eight patients with malignant lymphogranulomatosis

The isolated virus gave a positive serologic reaction with serum from a patient with sarcoidosis but the titers were low and may have been due to previous mumps infection In patients with sarcoidosis a cutaneous reaction was obtained with the killed virus Results were negative in a control group

[Hardly a year goes by without report of a new etiology for sarcoidosis —Ed]

Joint and Skeletal Muscle Manifestations in Sarcoidosis have received scant attention in the literature Only six cases of arthritis associated with and attributed to sarcoidosis have been found Gordon B Myers A M Gottlieb P F Mattman G M Eckley and J L Chason[7] (Detroit) observed four patients with migratory polyarthritis resembling rheumatic fever or rheumatoid arthritis and with histologic evidence compatible with sarcoidosis They report the cases to draw attention to the (1) association of sarcoidosis and polyarthritis and (2) value of muscle biopsy in diagnosis in cases of suspected sarcoidosis without cutaneous or lymphoglandular lesions

The four patients had in common (1) migratory febrile polyarthritis resembling rheumatic fever but refractory to salicylates (2) hilar lymphadenopathy consistent with Boeck s sarcoid (Fig 8) and (3) noncaseating epithelioid granulomas of sarcoid type (Figs 9 and 10) demonstrated by muscle

(7) Am J M d. 12 161 169 F b ry 1952.

F g 8—Ch t ay re eal g b l t al h l ! ; thy (C t y f My G B *et al* Am J Med 12 161 169 Febru y 1952)



F g 9 (l ft) —(t rc m m scl se t g g a f m d g muscle fibe s f Poeck s sa c d type
F g 10 (ght) —I sam p t t edz f n se t g g f m i oo t l nal i r led
(Cou te y f My (B *et l* Am J Med 1 161 169 F b y 2)

biopsy in three and by lymph node biopsy in one In addition erythema nodosum was present in three patients finely nodular pulmonary infiltrations in two generalized lymphadenopathy in two healed chorioretinitis in one and acute uveitis and parotitis in one

The possibility was considered that all features might be fitted into the syndrome of erythema nodosum since typical skin lesions were present in three cases and compatible hilar adenopathy was found in all four A search of the literature disclosed only two cases in which sarcoid like granulomas were demonstrated by skin biopsy in erythema nodosum On the other hand in a recent comprehensive review erythema nodosum was included as an authenticated manifestation of sarcoidosis

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IMMUNIZATIONS

Laboratory Comparison of United States and British Army Typhoid Paratyphoid Vaccine is presented by W Sloan Miller Donald L Clark and Othmar C Dierkhising[8] (U S Naval Med Research Unit No 3 Cairo Egypt) Apparently no large outbreaks of typhoid fever occurred in the U S Army during World War II nor in the past 30 years and there is a tendency to ascribe this to the effectiveness of anti typhoid inoculation In recent years the British armed forces especially those in the Suez Canal Zone have been less fortunate In an outbreak among British troops in Europe in 1944 79 men in a unit of 230 contracted typhoid fever and 9 died In an epidemic in the Suez Canal Zone in 1945 in an airmen s mess of 747 persons 110 (14 7%) had the disease and 11 (10%) died This outbreak was attributed to an Egyptian cookhouse employee who had heavy urinary excretion of typhoid bacilli In 1950 in another mess there were two separate outbreaks of typhoid In the first there were 96 typhoid patients of 639 people at risk an attack rate of 15% Two months later in the same mess there were 233 typhoid patients a rate of over 30% The laboratory comparison of potency of British and American vaccines was made knowing that British vaccines had failed to prevent typhoid fever

(8) Am J T p M d 31 535 551 S pt mb 1951

Results of the mouse protection tests indicate that the British Army alcoholized vaccine (BA) is superior to its equivalent phenolized vaccine (BP) Experimental findings reveal that the BA product is probably three times as effective volume for volume as the BP in protecting mice against a near lethal dose of typhoid bacilli In all seven valid experiments eight different samples of BA vaccine less than 2 years old were assayed On no one occasion was a dose of more than 0 0005 ml required to save 50% of the mice In the same experiments nine different samples of U S vaccine less than 2 years old were assayed under similar conditions Each time more than 0 01 ml was needed to effect the same response The BA vaccine is therefore probably at least 20 times as effective as the standard U S product

There is little doubt that British forces have been obtaining quantitatively much more immunogenic material for typhoid prophylaxis than is now customary in the American forces There is no means of knowing what recent British experience would have been if prophylactic inoculation had not been enforced The best statistical data available on incidence of typhoid fever among inoculated and uninoculated troops abroad are the figures collected by the British anti typhoid committee many years ago which indicate that vaccination may reduce incidence but do not suggest absolute immunity for the inoculated Recent experience of the infection as it occurs in and near Cairo indicates that something much better than ordinary TAB vaccine must be found before prophylactic inoculation can be described as effective in controlling typhoid fever in highly endemic areas

[The occurrence of serious outbreaks of typhoid fever among immunized persons is most disturbing The diminished prevalence of typhoid in this country is probably due more to sanitation than to immunization —Ed]

Immunization of Adults against Diphtheria and Tetanus Geoffrey Edsall[9] (Army Med Service Graduate School Washington D C) *notes that recently many reports have* appeared calling attention to the relatively high susceptibility of adults to diphtheria in North America Western Europe and Australia It is no longer plausible to assume that most adults are immune to this disease This increase in susceptibility is most likely due to the decrease in incidence The con

(9) Am J P b Health 42 393 409 Ap 1 1952

current decrease in the frequency of carriers signifies the marked diminution of the naturally occurring recurrent mild infections which have clearly been related to the maintenance of lasting immunity Although diphtheria has occurred in immunized persons in outbreaks among intermingled immunized and nonimmunized populations morbidity and mortality rates have been lower in the former

Immunizing procedures are relatively simple in children but administration of toxoid to an adult may put him to bed for three or four days with a massively swollen arm which may not return to normal for two weeks In general Schick negative persons are 3 10 times as prone to show local or general reactions as are Schick positive persons hence the problem of minimizing reactions in adults has been approached by preliminary Schick screening As the antigenic stimulus afforded by the first test may convert 25-45% of apparently Schick positive to Schick negative adults it is recommended that persons with positive reactions originally be retested In doing such work it has been found that a second Schick test will result in an antitoxin rise in 20 30% of those who remain positive In addition use of purified toxoid further reduces the frequency and severity of reactions in adults Also use of smaller doses of toxoid when tried have been unaccompanied by undue reactions Available evidence indicates that basic immunity will last three to four years on the average after a successful immunization To maintain a satisfactory level by repeated small doses is apparently feasible as investigators have shown that a fourfold reduction in dose will reduce the antibody response by only half Thus it is possible to maintain immunity by repeated small booster doses with a significantly reduced incidence of reactions

In the case of tetanus antitoxin prophylaxis has several faults It occasionally fails to protect its effect is transitory the horse serum invites a variety of untoward reactions and the antitoxin offers no protection to unrecognized injuries There is considerable evidence in favor of universal active immunization An effective schedule consists of primary inoculation and early booster and periodic booster doses thereafter including a booster dose at the time of injury Such a schedule should maintain adequate antibody levels for two to five years and obviate the need for antitoxin Although

not yet experienced the possibility always exists that repeated injections will produce sensitivity reactions of either the anaphylactic or the tuberculin type If the suggested schedule is followed more will be heard of this in the ensuing years

Poliomyelitis Occurring after Antigen Injections has been reported from various places Many cases of paralysis in a limb into which an antigen (or penicillin) was injected within the preceding 30 days are recorded Gaylord W Anderson and Audrey E Skaar[1] (Univ of Minnesota) report a study of 2 709 cases of poliomyelitis in Minnesota in 1946 Histories were taken by public health nurses and medical students an average of three months after the onset of illness Delay is felt to have enhanced the accuracy of information which was given by families probably more composed and co operative than in the initial phase of stress

Questioning revealed 85 medically confirmed and 42 un confirmed instances of antigen inoculation in the six months before poliomyelitis onset Of those medically confirmed 33 had had the most recent injection within the preceding month whereas 12 and 15 had had final injections two and three months before The concentration of incidence in the first preceding month suggests a causal relationship Further sug gestion of such relationship is the fact that 19 patients (58%) had subsequent temporary or permanent paralysis of the extremity into which the injection was given during the pre vious month whereas only 8 of the other 52 (15%) showed this correlation Also 20 (61%) of the 33 immunized in the preceding month had arm involvement as against 11 (21%) of 52 immunized two to six months before Of the 19 corre lated first month cases 7 had single extremity involvement 7 others had frank paralysis in the extremity used for injection plus some weakness in other areas and the other 5 had other associated sites of frank paralysis A definite tendency to more severe involvement of injected limbs is indicated Attempts to correlate type of antigen with results were not considered informative Diphtheria toxoid had been used in all but 1 of the 19 correlated cases yet diphtheria toxoid is the most extensively used antigen The supposed causal role of per tussis antigen not given to 10 of the 19 was not supported Age was important 19 (58%) of the 33 first month cases

(1) Pediatrics 7 741 759 Jun 1951

were under 2 whereas 19 (37%) of the other 52 were 2 or under

The authors conclude that since immunization is an elective procedure it can well be temporarily postponed during poliomyelitis outbreaks There is no evidence that antigen injection sensitizes a person to subsequent poliomyelitis attack for longer than one month

Effect of Pertussis, Diphtheria Toxoid and Salmonella Immunization on Experimental Poliomyelitis Because clinical evidence suggests that pertussis vaccine given alone or with diphtheria toxoid during the poliomyelitis season results in a significantly increased frequency and severity of paralysis in the inoculated limb Albert Milzer Molly A Weiss and Katherine Vanderboom (Michael Reese Hosp) studied the effects of these agents as well as of Salmonella typhimurium vaccine on Swiss mice inoculated intracerebrally with the Lansing strain of poliomyelitis virus Pertussis vaccine and alum precipitated diphtheria toxoid when given intraperitoneally alone or together significantly reduced the period before onset of paralysis The effects of intramuscular injection could not be studied in such small animals Similar results followed intravenous administration of Salmonella typhimurium vaccine but results with intraperitoneal inoculation were equivocal

Procaine penicillin G (30 000 units) in peanut oil given intraperitoneally at the same intervals as pertussis vaccine had no effect on the incubation period

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BIOLOGIC WARFARE

Potentialities of Biologic Warfare against Man An Epidemiologic Appraisal by Alexander D Langmuir[3] (Atlanta Ga) emphasizes two major forms of biologic warfare attack which are possible the creation of clouds of pathogenic aerosols over cities and the intentional contamination of water or food supplies or the air of strategic buildings

The importance of air as a medium of spread of naturally occurring disease has long been disputed The weight of

( ) P S E B l & M d 77 4 5 498 J l 1951
(3) P b H lth R p 66 387 399 M 30 1951

not yet experienced the possibility always exists that repeated injections will produce sensitivity reactions of either the anaphylactic or the tuberculin type If the suggested schedule is followed more will be heard of this in the ensuing years

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(1) Ped 1 cs 7 41 759 J e 1951

by known breaks in the skin as in cutaneous tularemia of rabbit hunters Inhalation of such infectious agents in particles so fine as to reach the alveoli thus becomes equivalent to subcutaneous inoculation These diseases are highly localized in distribution and a high proportion of this country s population is known to be susceptible They form a group that should receive first consideration as agents which might be employed in biologic warfare Artificial circumstances present an entirely different picture With modern laboratory technics many pathogenic agents may be grown in almost limitless quantities and dispersed into the air as single cells When this occurs accidentally as in laboratories a wholly artificial man made situation is created whereby such infectious particles may reach the alveoli The purposeful creation of such clouds is biologic warfare

An enemy might use air borne infection in biologic warfare against man without involving any new principles If grinding infectious tissue in a Waring Blendor will contaminate a room or if concentrating a suspension of pathogenic agents in a centrifuge will contaminate an entire building such circumstances could easily be reproduced Then with atomizers or other disseminating devices far greater concentrations of infectious aerosols could be produced Simple equipment portable in an ordinary suitcase would be sufficient A saboteur could contaminate air in any enclosed space where people congregate and anticipate a high attack rate of disease These same principles apply on a larger scale to the use of aerosol clouds over cities Specially designed bombs shell or other devices discharged from aircraft or warships offshore could create large clouds

Long familiarity with and understanding of epidemics caused by contaminated water and food supplies make it easy to comprehend how purposeful and malicious contamination could occur Experience with typhoid fever was long and bitter until standards of purity and safety of water supplies were universally established Concentration of pathogenic agents in naturally polluted waters is usually quite low compared to the wide variety of nonpathogenic flora normally present nevertheless serious epidemics have occurred Intentional introduction of a small volume of essentially pure pathogenic agent in highly concentrated suspension could

evidence however has suggested that most pathogenic bacteria either rapidly die or lose their virulence when exposed to air Attitudes of most informed workers have veered strongly away from the concept of air borne infection and toward the concept of contact and droplets It remains to be proved that air is an important medium for the spread of naturally occurring disease

Research scientists have long been aware of accidental infection as an occupational hazard and have willingly accepted it as a calculated risk Many different pathogenic agents are notorious offenders Attack rates have been high and many fatalities have been recorded Agents include those causing brucellosis tularemia Q fever typhus fever Rocky Mountain spotted fever psittacosis yellow fever and certain of the encephalitides coccidioidomycosis and others Numerous laboratory infections have occurred despite apparently flawless technic and meticulous precautions These incidents were explained obscurely and were generally dismissed by the general concept that such agents were extraordinarily infectious or had the capacity to penetrate through unbroken skin Although contamination of the air was sometimes postulated many research workers were reluctant to accept this inference Of special interest are the occasional explosive epidemics in research laboratories where many people in widely separated rooms are involved under circumstances which adequately preclude direct contact

The relation of size of inhaled particles to depth of penetration and retention in the respiratory tract has unique application in the theory of biologic warfare Particles more than 5 microns in diameter are almost completely removed in the nose and upper respiratory passages Progressively increasing proportions of smaller particles reach the terminal bronchioles and alveoli when inhaled and 50-60% of those near 1 micron in diameter penetrate to and are trapped in the alveoli More particles smaller than 1 micron are exhaled and alveolar deposition again decreases

In contrast many infectious agents particularly those known to be serious laboratory hazards do not ordinarily invade these sites in the upper respiratory tract the natural form of infection being direct inoculation by insect bite as in typhus Rocky Mountain spotted and yellow fevers or

The Chest

J BURNS AMBERSON M D

effectively contaminate a large section of a water distribution system and could be done by any person with minimal knowledge of sanitary engineering Food borne epidemics commonly result from contamination of certain types of warm or moist foods By inoculating a high concentration of certain pathogenic agents in appropriate food at the appropriate time a saboteur could almost certainly produce epidemics with high attack rates among the consumers

Sabotage methods would not necessarily be limited to use of biologically living agents Toxins of Clostridium botulinum or other bacterial or vegetable toxins or any of a wide variety of chemical poisons might similarly be utilized Biologic agents however have distinct advantages in that the extended incubation period of many hours days or even weeks would enable the saboteur to act and disappear whereas the more immediate reactions to chemical poisons might complicate his work

The epidemiology of air borne infection and of common vehicle epidemics forms the basis for developing a theory of biologic warfare Evidence supports the conclusion that biologic warfare could be employed effectively and therefore planning appropriate defenses cannot be delayed

[This article is of special interest since it was written before the claim was made that U N forces had used biologic warfare in Asia —Ed]

PART II

THE CHEST

ANATOMIC STUDIES

Anatomy and Applied Anatomy of Mediastinal Fascia Paul Marchand[1] (Johannesburg Hosp) dissected 12 human heart and lung specimens after subfascial peritracheal and hilar infiltration of colored radiopaque material to demonstrate extensions of the mediastinal fascia In neither neck nor mediastinum is the fascia solely pretracheal forming instead a complete investing layer to both trachea and esophagus In the neck the anterior part of this perivisceral fascia is thin and fibrous but becomes thicker and fibrofatty as it passes into the thorax The posterior aspect is closely but loosely applied to the tough prevertebral fascia Below the carina the anterior aspect of the perivisceral fascia sweeps on to the upper posterior surface of the pericardium to become continuous with the fibrous layer of the parietal pericardium Around the origin of the aorta anteriorly the fibrous and serous layers of the parietal pericardium are separated by loose connective tissue Over the ventricles however the two layers are so firmly adherent that separation is only possible by sharp dissection The great vessels except the inferior vena cava are invested in their extrapericardial course by fascial sheaths derived from the fibrous layer of the parietal pericardium The fascial sheaths of the pulmonary arteries and veins are prolonged around these vessels into the lung The perivisceral fascia is prolonged laterally as a fibrous investing layer of the left and right bronchi It is readily separated from the extrapulmonary bronchi and within this plane the bronchial artery lymphatic vessels and nodes are situated Separation of fascia from bronchus becomes more difficult the farther the lung is penetrated Below the carina the perivisceral fascia continues as an investing layer of the

(1) Th 6 359 368 D mb 1951

the underlying lung Often one branch of the hilar pleural vessels extending to the apical pleura was observed The true bronchial arterial divisions radiated along the major bronchi adhered closely to the bronchial tree and followed the same course They bifurcated with the bronchi and sent two divi sions along each bronchus one on each side of its wall which often tended to form an intercommunicating network in the fibrous coat of the bronchus Smaller twigs penetrated the bronchial walls and appeared as a similar network in the sub mucosa No precapillary anastomoses could be demonstrated between the bronchial and pulmonary arteries

The injected lungs were inflated via the trachea with 10% formol saline suspended in the same solution for 48 hours and examined histologically In all bismuth filled ar teries were seen in the capsule and stroma of hilar lymph nodes In seven the vasa vasorum to the pulmonary arteries could be identified and were seen to be well filled with bismuth In five sections of the vagi from the region of the major bronchi well filled bronchial arterioles were seen in the peri neurium No uninjected arterioles were visible near the nerve trunks The main bronchi in transverse section usually re vealed three to four large bronchial arteries in the peri bronchial coat Branches passed through the cartilaginous gaps and after supplying the perichondrium entered the tunica propria as small but obviously injected vessels In the smaller bronchi the arterial arrangements were the same but vessels were of smaller caliber Distribution to the struc tures of bronchial walls was also the same In the region of the bronchioles small bronchial arterioles were seen within and *without the bronchiolar walls* Well *injected bronchial* arterioles were seen in the interlobular septa Near the alve olar ducts the smallest bismuth filled arterioles were seen adjacent to the mucosa diameter was probably just over 80 μ Corresponding pulmonary arterioles and venules were larger and free from bismuth Larger well filled bronchial arterioles were however visible in the supporting framework of the alveolar epithelium and appeared to enter the air sacs with strands of elastic tissue which insinuated themselves between the alveoli as outgrowths of the interlobular septa

[Interest in distribut on of bronchial arteries and their circulatory function has grown of late particularly since this circulation plays an

esophagus to blend eventually with the outer coat of the stomach

Prolongation of the perivisceral fascia around the bronchi *into the lung substance forms a potential space which can be* occupied by air or exudate and connects lung and mediastinum This space may account for mediastinal emphysema which follows injury to a bronchus such as chest stab wounds without pneumothorax (because of pleural adhesions) *or rupture of a bronchus during labor* Similarly spontaneous mediastinal emphysema may be due to rupture of an alveolus or an emphysematous bulla into the peribronchial or perivascular fascial planes

[The implication of this study in clinical practice is obvious Familiarity with the anatomy of fascial planes helps to explain not only the path of travel of leaking ga or air but also that of fluid collections from various sources —Ed]

Observations on Normal Anatomy of Bronchial Arteries L Cudkowicz and J B Armstrong (Postgraduate Med School London) outlined the bronchial arteries in 10 normal lungs by injecting a contrast medium into the aorta under pressures *equal to the mean systolic pressure recorded during* life and taking radiographs The bismuth injection medium filled vessels of 60μ or more in diameter In some instances the relation of the bronchial arteries to the bronchi was further defined by injecting the bronchial tree directly

Bronchial arteries emerged in *varying numbers* often two *to each lung from the inferior aspect of* the arch and the descending aorta *Origins from sources other than the aorta* were not noted Before reaching the hili the arteries ran laterally from the aorta and crossed the esophagus anteriorly or posteriorly In their path from the aorta to the hilus they sent branches to the mediastinum esophagus hilar lymph *nodes and vagi On reaching the main bronchus on each side they formed an annulus surrounding the bronchus* and *from this structure the true bronchial and pleural arteries* emerged

The medial pleura received vessels directly from the annulus The anterior lateral and interlobar visceral pleurae received arteries from branches of the bronchial arteries within the lung substance These vessels visible to the naked eye appeared over the lateral pleura after emerging from

( ) Th 6 343 358 December 1951

on completion of the timed interval Thus the added pointer recorded timed volume and the standard pointer of the instrument recorded total vital capacity

Normal volunteers were able to expire 83 per cent of total vital capacity during the first second of effort 94 per cent during the first two seconds and 97 per cent during the first three seconds Total vital capacity was severely reduced in patients with restrictive ventilatory insufficiency but timed percentages remained essentially normal In patients with obstructive insufficiency total vital capacity was not markedly reduced but percentages of the total vital capacity expired during the first three seconds were sharply reduced In 28 bronchial asthma patients these percentages were 43 59 and 71 for one two and three seconds The same percentages in 40 patients with pulmonary emphysema were 42 57 and 68 Unlike total vital capacity the timed capacities correlated very well with maximum breathing capacity air velocity index and the residual volume/total capacity ratio Expiratory patterns of the same patients on repeated occasions varied very little Unlike the total vital capacity timed capacities were most sensitive indicators of an artificially introduced stenosis of the airway Timed vital capacity should be useful in hospital and physician s office in screening studies and large scale investigations where a simple and inexpensive method for ventilation analysis is needed

Anoxia and Human Pulmonary Vascular Resistance were studied by Richard N Westcott Noble O Fowler Ralph C Scott Virgil D Hauenstein and Johnson McGuire[4] (Univ of Cincinnati) by means of cardiac catheterization in 27 subjects of whom 20 were normal 4 had left ventricular failure 2 pulmonary emphysema and cor pulmonale and 1 pulmonary fibrosis Breathing of 13% O_2 produced (1) average rise in mean pulmonary artery pressure of 24 6% above control levels on 26 occasions (2) no significant change in mean pulmonary capillary pressure in 16 subjects (3) no significant change in cardiac output in 13 subjects in whom multiple Fick determinations were made Simultaneous determinations of mean pulmonary artery and pulmonary capillary pressures and cardiac output were made before during and after 13% O_2 breathing in 10 subjects Pulmonary arteriolar resistances

(4) J Cl I t 30 957 970 S pt mb 1951

important part in many pulmonary diseases Bronchial artery circulation has been demonstrated to be of vital importance to nutrition of the major bronchi —Ed]

PHYSIOLOGIC MECHANISMS

The study of physiologic mechanisms in cardiorespiratory function has been active and productive An understanding of physiology is of course basic in a comprehension of disease processes and their control —Ed

Analysis of Ventilatory Defect by Timed Capacity Measurements The lung's *maximal ventilation capacity* depends essentially on two factors (1) total gas volume or maximal stroke volume displaceable by a single maximal respiratory effort and (2) speed at which this volume can be exhaled Speed depends on the resistance to air flow offered by the respiratory passages and that to change in shape offered by lungs and thorax The resistance factors determine the time required to complete the maximal expiratory effort Vital capacity does not effectively measure this since a patient with a normal stroke volume and a large resistance factor eventually expires a normal amount of air if he abstains long enough from drawing another breath Normal ventilatory function depends on both adequate stroke volume and absence of abnormal resistance factors This explains the failure to correlate vital capacity with true tests of maximal ventilation Edward A Gaensler[3] (Harvard Med School) describes an attachment for the standard vital capacity spirometer which automatically records both total vital capacity and any volume expired during a pre set interval of 0 1 to 10 seconds

METHOD —The only part modified was the volume recording wheel to which three additions were made A second pointer moved by the small rod of a miniature solenoid rather than by the stop on the wheel was added to the scale As soon as current to the solenoid (the second addition) was interrupted the rod retracted and the second pointer stopped moving A microswitch which closed as soon as the wheel began to turn was also added The spirometer with these attachments was used in conjunction with an electronic timer which permitted selection of intervals from 1 to 10 seconds The microswitch initiated the timing cycle with the patient's expiratory effort the solenoid activated for the duration of the timing cycle moved the second pointer on the scale The solenoid was inactivated and the second pointer came to rest

(3) Am R T be 64 56 78 Septembe 1951

on completion of the timed interval Thus the added pointer recorded timed volume and the standard pointer of the instrument recorded total vital capacity

Normal volunteers were able to expire 83 per cent of total vital capacity during the first second of effort 94 per cent during the first two seconds and 97 per cent during the first three seconds Total vital capacity was severely reduced in patients with restrictive ventilatory insufficiency but timed percentages remained essentially normal In patients with obstructive insufficiency total vital capacity was not markedly reduced but percentages of the total vital capacity expired during the first three seconds were sharply reduced In 28 bronchial asthma patients these percentages were 43 59 and 71 for one two and three seconds The same percentages in 40 patients with pulmonary emphysema were 42 57 and 68 Unlike total vital capacity the timed capacities correlated very well with maximum breathing capacity air velocity index and the residual volume/total capacity ratio Expiratory patterns of the same patients on repeated occasions varied very little Unlike the total vital capacity timed capacities were most sensitive indicators of an artificially introduced stenosis of the airway Timed vital capacity should be useful in hospital and physician s office in screening studies and large scale investigations where a simple and inexpensive method for ventilation analysis is needed

Anoxia and Human Pulmonary Vascular Resistance were studied by Richard N Westcott Noble O Fowler Ralph C Scott Virgil D Hauenstein and Johnson McGuire[4] (Univ of Cincinnati) by means of cardiac catheterization in 27 subjects of whom 20 were normal 4 had left ventricular failure 2 pulmonary emphysema and cor pulmonale and 1 pulmonary fibrosis Breathing of 13% O_2 produced (1) average rise in mean pulmonary artery pressure of 24 6% above control levels on 26 occasions (2) no significant change in mean pulmonary capillary pressure in 16 subjects (3) no significant change in cardiac output in 13 subjects in whom multiple Fick determinations were made Simultaneous determinations of mean pulmonary artery and pulmonary capillary pressures and cardiac output were made before during and after 13% O breathing in 10 subjects Pulmonary arteriolar resistances

(4) J Cl I t 30 957 970 S pt mb r 1951

showed average increase of 48 5% during low oxygen breathing a highly significant difference Ballistocardiograms showed relatively normal complexes during control observations on most normal subjects However during and after 13% O breathing the complexes invariably became abnormal in such a way that quantitative calculations were impossible Whether these changes were due to the direct effect of anoxia on myocardium could not be established In 12 subjects arterial O_2 saturation was reduced an average of 13 1% during 13% O breathing In individual cases there was no direct correlation between specific value to which arterial O_2 saturation was depressed and observed elevation of pulmonary artery pressure or pulmonary arteriolar resistance

Anoxia caused prompt increase in pulmonary vascular resistance which was in turn rapidly dissipated when anoxia was relieved This increase in resistance to blood flow must have resulted from vasoconstriction It was not determined whether this vasoconstriction is mediated through the autonomic nervous system or depends on a direct local effect on the pulmonary vessels It seemed that if one component of chronic pulmonary hypertension is anoxic vasoconstriction breathing 100% O should reverse this effect at least in part The effect on pulmonary artery pressure of 10 20 minutes of 100% O breathing was therefore recorded in nine subjects two were normal one with compensated systemic hypertension one with early pulmonary fibrosis and five with chronic pulmonary hypertension with cor pulmonale A slight rise or no change in mean pulmonary artery pressure was found in the subjects with normal control values definite decline was noted in the five with chronic pulmonary hypertension in three of whom it returned to previous elevated levels soon after ambient air was breathed Although cardiac output was not determined and the number of cases was too small for statistical analysis results were consistent with the possibility that anoxic elevation of pulmonary arteriolar resistance may be a contributing and reversible factor in production and maintenance of at least some types of chronic pulmonary hypertension

Reduction of Blood Flow through the Hypoxic Lung Individual lung blood flows were measured by R J Atwell J B Hickam W W Pryor and E B Page[5] (Duke Univ) in six

(5) Am J Physiol 166 37-44 July 1951

dogs by the Fick principle while the lungs were breathing separately through a bronchospirometric catheter When one lung was brought into gaseous equilibrium with the pulmonary arterial blood by rebreathing while the other lung continued to breathe air half the animals showed a well marked shift of pulmonary blood flow toward the air breathing lung and away from the rebreathing lung Mean pulmonary arterial pressure was significantly higher in the rebreathing periods Generally pulmonary venous pressures did not rise during re breathing but measurement was not totally satisfactory

Rebreathing involved local elevation of carbon dioxide tension and decreased oxygen tension In cats and dogs pre viously observed inhalation of carbon dioxide caused vaso constriction in the isolated perfused lung and increased car bon dioxide tension may be a factor in the production of shunting

Adaptation to Anoxia in Chronic Pulmonary Emphysema Russell H Wilson Craig W Borden and Richard V Ebert[6] (Minneapolis) studied 69 male patients In contrast with resi dents of high altitudes increased hemoglobin content of blood was seldom observed Moreover there was no evidence of in creased activity of bone marrow in the 14 patients tudied The reason for this failure of hematologic adaptation to anoxia was not established but it may be related to presence of chronic bronchial infection A decreased serum iron value has been reported in association with chronic infection and anemia In eight patients mean serum iron value was 102 ± 26/100 cc mean normal value for the laboratory was 122 ± 38/100 cc On the other hand mean corpuscular vol ume was regularly increased and apparently the result of anoxia

Pulmonary Function Studies in Sarcoidosis E Osborne Coates and Julius H Comroe Jr[7] (Univ of Pennsylvania) studied eight patients with pulmonary involvement In three radiologic studies demonstrated intrathoracic lesions confined largely to enlargement of the hilar and mediastinal lymph nodes and physiologic findings were normal except for slightly reduced maximal breathing capacity per minute in one patient and low arterial oxygen saturation in another

(6) A M A A h I t M d 88 581 590 N mb 1951
(7) J Cl I t 30 848 85 A gu t 1951

Of five patients with parenchymal involvement of the lungs vital capacity was significantly reduced in three largely through diminution in inspiratory capacity Total lung capacity was below the predicted normal in only one patient In all five residual volume increased markedly, varying from 160 to 331 per cent of the predicted normal value The residual gas volume/total capacity ratios were 30-65 per cent all abnormally high Similarly the functional residual capacity (sum of residual gas volume and expiratory reserve) was above normal in all The lungs were thus in a hyperinflated state after both forced and normal expiration All five evidenced impaired mechanics of breathing maximal breathing capacity was 56 74 per cent of expected normal Distribution of inspired gas to the alveoli as judged by the single breath analysis was definitely abnormal in all five even though pulmonary nitrogen elimination was normal as judged by the Cournand seven minute test This emphasizes the greater accuracy and reliability of the single breath test as a measure of uniformity of distribution of inspired gas Only one patient had pulmonary insufficiency at rest for the oxygenating mechanism none had insufficient carbon dioxide elimination None had disabling dyspnea Apparently breathing could be increased enough to arterialize venous blood without severe discomfort These results differ from those of other authors probably because of case selection

Roentgen examination in these patients was unreliable as a guide to functional impairment considerable change in function studies and in clinical symptoms might occur with little change in the x ray appearance

Clinical and Physiologic Features of Some Types of Pulmonary Diseases with Impairment of Alveolar Capillary Diffusion Syndrome of 'Alveolar Capillary Block" *Robert Austrian John H McClement Attilio D Renzetti Jr Kenneth W Donald Richard L Riley and Andre Cournand*[8] (Columbia Univ) studied 12 patients with various diffuse diseases of the lungs characterized physiologically principally by interference with diffusion of oxygen across the alveolar capillary septum The group included two with pulmonary granulomatosis following exposure to beryllium one with pul

(8) Am J Med 11 667 685 Dec mb 1951

monary granulomatosis of the Boeck sarcoid type and one with pulmonary granulomatosis of undetermined cause one with scleroderma three with pulmonary fibrosis of unknown cause (in one after exposure to beryllium) and four in whom a diagnosis could not be made The striking physical signs and symptoms included tachypnea at rest limited excursion of the thorax presence of persistent fine rales heard usually over the lower lobes and accentuation of the second pulmonic heart sound Cyanosis significantly was absent or of minimal degree at rest except in terminal stages but appeared rapidly on mild exertion Clubbing of fingers was noted occasionally

Measurement of lung volumes showed significant reduction in total pulmonary capacity in general associated with parallel reduction in each of its subdivisions As a result ratio of residual volume to total capacity remained normal in all but three patients and even in these obstructive emphysema was not present Maximal breathing capacity was close to normal in almost all patients and in fact was greater than the predicted value in 7 of the 12 Increased physiologic dead space was noted in most patients By constant hyperventilation normal or increased values for effective alveolar ventilation were maintained even in those with a very large physiologic dead space In all but three patients despite a large maximal breathing capacity this hyperventilation resulted in abnormal reduction of the breathing reserve especially during exercise and recovery from exercise

Arterial oxygen saturation fell from a normal or minimally reduced value at rest to a distinctly low value during exercise In every patient calculated alveolar oxygen tension was normal and in several exceeded the normal level Alveolar arterial oxygen tension gradient was increased above normal in all patients when breathing room air at rest and an abnormally large gradient was noted when breathing an atmosphere with oxygen concentration lower than that of ambient air In most cases alveolar arterial oxygen gradients measured at two levels of inspired oxygen concentration were of nearly equal magnitude Oxygen diffusing capacity was lower than normal under resting conditions in the 11 patients in whom it was measured Calculated venous admixture was significantly increased in 9 of the 11 patients The hemodynamics of the

pulmonary circulation revealed a mild to striking degree of hypertension in the pulmonary artery in all patients in whom measurements were made during steady mild exercise Cardiac output at rest was normal or increased in all patients without congestive failure and was significantly decreased in two when it was measured during cardiac decompensation Increase in cardiac output during mild exercise was in the expected range

Disability was related neither to reduction of lung volume nor to maximal breathing capacity Residual volume/total capacity ratio was increased in some patients with the most severe disease Increasing disability from this syndrome seemed related to appearance of arterial oxygen unsaturation at rest and in the final stages to a return of the usually low arterial carbon dioxide tension at rest to normal or slightly increased levels The patients with more advanced disease had in general a large physiologic dead space and venous admixture and there was some relation between severity of the disease and degree of reduction of oxygen diffusing capacity

Lung Function Studies VII Effect of Pneumonectomy on Respiratory Dead Space Ward S Fowler and William S Blakemore[9] (Univ of Pennsylvania) studied the respiratory dead space in eight patients (one of them female) after pneumonectomy for pulmonary neoplasm seven were also studied a few days preoperatively Eleven elderly (aged 53 71) male hospital patients without clinical or fluoroscopic evidence of pulmonary disease served as controls All were examined semireclining in bed with head and trunk elevated 50 60 degrees Subjects were not in basal condition but had bed rest for at least 10 minutes before measurement Postoperatively three showed no change and four male patients showed significant reductions The mean postoperative values for dead space (149 ml) and dead space/tidal volume fraction (26 6 per cent) were similar to control values for the elderly men

Bronchographic Studies in Dyspnea P L Martin[1] (Bordeaux) after basal and topical anesthesia instilled 40%

(9) J Th c S g 21 433 437 May 1951
(1) J rad ol t él tr 1 3 577 583 1951

lipiodol® through the endotracheal tube with the patient in lateral decubitus In normal subjects films taken in forced expiration and inspiration showed doubling in size of segmental bronchi Within a few minutes the medium had left the bronchi and penetrated alveoli coughing hastened the process and produced immediate dissemination of the medium throughout the alveoli In asthmatic patients studied between attacks the oil sta nated in the larger bronchial trunks inspiratory inflow stopped at the level of branches



Fg 11—R d t f l b fil f m b h Two-th d t l (C y f M t P L J d l t l t l 3 77 583 1951)

of the fourth order The lumens of segmental bronchi were greatly reduced This diminution characteristically was smooth all along the spasmodic bronchus and was abrupt without transition toward the proximal bronchus which remained normal in caliber At times the bronchi were filiform in appearance (Fig 11) These changes were observed on fluoroscopy In addition to the regular longitudinal diminution of caliber x rays showed an abrupt ending of the bronchi as if their peripheral parts were amputated Parenchymatous diffusion was seldom or never seen Bronchial caliber hardly changed between full expiration and inspiration (Figs 12 and 13) Coughing forced the oil into the trachea and it

was expectorated rather than dispersed throughout alveoli (parenchymatous expulsion)

These changes were not absolutely correlated with asthma in numerous asthmatic patients dyspnea is caused by secretions and swelling of the bronchial mucosa without spasm On the other hand in patients poorly prepared or particularly sensitive the procedure brought on asthma like dyspnea In emphysema bronchographic changes were seen but in these there was also some isolated dispersion of medium



Fig 12 (left) —I p at n Two-th rds tu l s ze
Fig 13 (ght) —L p t ab nce f n rmal var at n cal be sp to y mmol l ty
(Cou te y f M rt P L J r d l et el ct l 3 577 583 1951)

through parenchyma on coughing the bronchial walls had a crenated appearance on the bronchogram (due to bronchorrhea) and usual radiologic signs were present In chronic bronchitis the same changes may appear and parenchymatous expulsion on coughing may be spectacular but crenation of the bronchial wall due to predominant bronchorrhea is undeniable

In general caution must be used before bronchial amputation and parenchymatous expulsion are attributed to bronchospasm A typical bronchographic picture has been seen when bronchoscopy showed merely mucus thickening and hypersecretion

Results of Re-examination by Mass Radiography in which more than 45 000 individuals were rescrutinized in two years are reported by V H Springett[2] (Royal College of Physicians London) The unit was static comprised of civil servants in the London area Previous examination at the unit had been noted so that by review of record cards those previously examined in the same place could be grouped by age and sex Those x rayed earlier elsewhere were grouped as not previously examined Subjects in whom tuberculosis was found were also classified on the basis of rescrutiny of the previous film for earlier tuberculosis From records on civil servants who after a normal examination developed clinical tuberculosis and were therefore not re examined incidence of tuberculosis could be approximated although the two groups were not exactly coextensive

New lesions were found in 4 7 of 1 000 males examined at ages 15 24 but declined with increasing age to 1 7 per 1 000 at ages 45 59 At ages 15 24 6 8 of 1 000 females and between ages 45 and 59 less than 1 of 1 000 showed lesions Expressed as annual attack rates the results were Women—3 5 per 1 000 at 15 24 years 2 per 1 000 at 25 34 0 5 per 1 000 over 34 men—3 per 1 000 at 15 24 years 2 per 1 000 at 25 34 1 per 1 000 at 45 59 These rates were low estimates as no allowance had been made for clinical tuberculosis patients who had not been re examined radiologically Although attack rates could not be calculated from these clinical patients the age distribution coincided with that in mass radiography In men most of those with active disease at the second examination and definite lesion on previous examination were in the older age groups and they had had a type of disease usually recognized as stable Their importance was emphasized by the fact that there were 21 active cases in males aged 35 or over who had shown lesions in previous examination while 14 in this age group with previously normal film now showed active disease Only two women aged 30 and 34 were assessed as active after having been previously regarded as stable

(2) B t M J 2 144 148 J ly 21 1951

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F g 12 (l ft) —In p t n Two-th d act al
F g 13 (ght) —Exp t n b ce of n m l at on n cal ber p to y mmob l ty
(C t y f M t P L J d l t l t ol 32 577 583 1951)

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[2] Br M J 144 148 July 21 1951

In summary repeat mass radiography examinations show the highest incidence of new lesions in young adults of both sexes As few new cases appear in older males and practically none in older females the maximum attendance of young adults for repeat examinations should be the main goal Further supervision should be arranged for apparently healed or healing disease in older persons particularly males however discovered Special arrangements for repeated examination of such patients by mass radiography is unsatisfactory as it is difficult to compare two 35 mm films

[A number of questions have been raised regarding x ray surveys and their relative value in a public health program—Ed]

Clinical and Experimental Studies in Use of Water soluble Agent for Bronchography Mordant E Peck A J Neerken and Emanuel Salzman[3] (Univ of Colorado) report use of 1 75% solution of methylcellulose in 50% diodrast® Under sodium pentothal anesthesia a single intratracheal injection was given 10 dogs autopsy 48 72 hours later showed gross and microscopic evidence of bronchopneumonia in 2 However it is difficult to compare the tracheobronchial physiology in the dog with that of man Of six dogs similarly treated with iodochlorol® (analogous to lipiodol®) frank bronchopneumonia developed in three and the others had evidence of peribronchial infiltration Therefore it was felt safe to proceed with experimentation in human beings No allergic reactions were noted only patients with negative skin reactions to diodrast® were given this material

Bronchograms obtained with the methylcellulose diodrast® mixture differ in some respects from those obtained with lipiodol® It tends to adhere to the bronchial mucosa causing visualization of the bronchial tree largely in mucosal relief and revealing small filling defects which might not be observed by the complete filling common with iodized oil The medium mixes readily with bronchial secretions and thereby outlines partially filled bronchiectatic areas Iodized oil frequently *separates into droplets and incomplete visualization of* involved bronchi results Since diodrast® is rapidly absorbed films must be made within two to three minutes after its instillation Films made after a longer interval appear blurred

(3) S g Gy ec & Ob t 92 685 69 J 1951

Iodized oil permits a longer interval between instillation and exposure of films However once one becomes accustomed to the medium more information can be obtained than with lipiodol ® Initial results were so satisfactory that the authors



F g 14 (l ft) —Cyl d b h t f l w l b b h
F g 15 (b l w l ft) —Abd men hou ft b hog pby
F g 16 (b l w) —L g 24 h l t
(C t y f P k M E t l S g Gy & Ob t 9 695 69 J 1951)





now use this solution routinely in bronchographic studies (Figs 14 15 and 16)

[Newer mediums for bronchography are of incr asing interest be cau e they are rapidly abso bed On this account observations mu t be made and roentgenograms taken within a very short time Con equently iodized oil is still preferred when several diff rent views are re qui ed —Ed]

Influence of Position on Breath Sounds Auscultation of the chest was performed by Andrew Kerr Jr[4] (Tulane Univ) on 58 men and women upright and in both recumbent positions Of these 11 had pulmonary disease and 8 had extremely enlarged hearts the others had no heart or lung abnormalities Each was first examined on the left side

Thirty six of the normal subjects and seven with pulmonary disease whose breath sounds were equal on both sides when upright showed on changing position an increase in both intensity and pitch of the inspiratory note at the base posteriorly on the dependent side Diminution of the breath sounds on the opposite side in a comparable area was noted In a few the breath sounds were almost absent over the upper base Inconstant changes were noted in three normal subjects in four of the seven pulmonary patients and in all eight of those with enlarged hearts Particular attention was focused on the expiratory murmur and in only 11 of the 58 examined was any increase in pitch duration or intensity noted Auscultatory sounds unless the patient is upright should be interpreted with caution

[Variations in quality and intensity of breath sounds are not given the value in diagnostic examinations which was once the custom This of course is due mostly to dependence on x ray examination Nevertheless there are situations in which the variations of breath sounds may be interpreted with great advantage in clinical understanding —Ed]

Significance of Calcification in Pulmonary Coin Lesions Hans Abeles and Aaron D Chaves[5] (Dept of Health New York City) report experience with 13 pulmonary coin lesions with calcifications demonstrated roentgenographically Five lesions were excised—three hamartomas and two tuberculomas Two of the hamartomas had shown concentric growth over several years but the patients at first refused operation The other eight lesions remained unchanged for 2 12 years No patient had signs or symptoms of malignant disease All 13 were asymptomatic Eight were over 40 and 12 were males

Demonstration of calcification within a pulmonary coin lesion may be considered strong evidence that the lesion is not malignant The generally accepted routine excision of solid circumscribed pulmonary lesions should not be applied to lesions with calcification Rare exceptions such as broncho

(4) N w F gl nd J M 1 45 58 59 J ly 1 1951
(5) Rad logy 58 199 203 Febru y 1952

genic carcinoma enveloping a calcified tuberculous focus and some forms of sarcoma do not warrant routine removal of coin lesions with demonstrable calcification Every effort should be made to detect calcification in all coin lesions using sectional radiography routinely By this means information is easily obtainable which may justify periodic supervision rather than immediate excision in patients who are poor operative risks

[This study represents an effort to make finer distinctions in the diagnosis of sph rical l sions of the lung The conclusion that demonstrable calcification can be taken as evidence of nonmalignant disease is sound The lesions are usually inflammatory most often tuberculous some should be removed surgically but not necessarily all —Ed]

PNEUMONIA

Explanation of "Primary Atypical Pneumonia" Syndrome Philip W Robertson and K D Forgan Morle[6] (Liverpool) observed 500 young men in initial basic military training Nearly all had radiologically normal chests on entry a few cases were disclosed by mass miniature radiography There was no constant clinical picture as the illness varied greatly in intensity and duration Most patients were moderately ill the first 24 48 hours some were seriously ill but none died Most were febrile and felt miserable their discomfort being aggravated by pain and cough A few days after onset of upper respiratory infection one or more cardinal signs of pulmonary disease developed Cough was invariable often characteristically harsh and repetitive Sputum was usually absent or scanty in the early stages but was present later often yellowish green and obviously purulent blood staining was frequent Chest pain was common and often pleural Dyspnea was rare Fever was often quite high initially but soon subsided occasionally followed by a second rise in temperature

There was always an upper respiratory infection either at the height or in the decline of the disease Physical examination seldom revealed any generalized chest disease Sputum culture usually showed a heavy growth of organisms normally found in the upper respiratory tract Total white cell count

(6) B M J 2 994 998 Oct 27 1951

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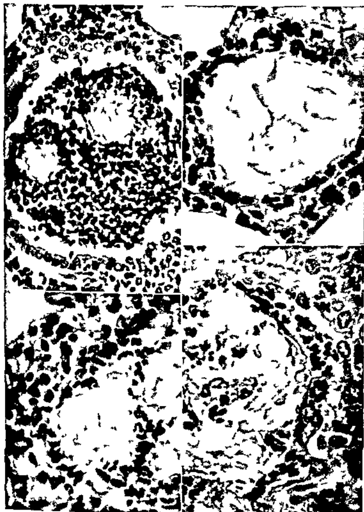
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(4) New F gl d J Med 45 58 59 J ly 12 1951
(5) R d ology 58 199 203 Febr y 195



F g 17 (t p l ft) — ta h ll und d by gm t d t ph l n b n h l

F g 18 (t p ght) —N w m f gm t d eut ph l ou d t h ll

F g 19 (b ttom l ft) —S gm t d t ph l tend g th gh ll w ll lay f mo ocyt d lymphocyt ou d m f segm t d t oph l mm d t ly ou d food

F g 0 (b ttom ght) —S gm ted t ph l d d g t d food p t l monocyt d lymphocyte ght ound m f gment d t ph l l g ts d f food pa t l

(Cou t y f M T J A M A A h. P th 5 350 354 Octobe 1951)

was rarely significantly raised usual range being 7000-14000/cu mm Sedimentation rate occasionally estimated was usually raised sometimes considerably

The one constant feature was anatomic localization to bronchopulmonary segments or subsegments so that radiologic appearances depended on the portions of lung involved To define the site and extent of the lesions and to see some retrocardiac and basal lesions at all lateral films were essential Every degree of abnormality was seen from dense ground glass opacity to increased density of the bronchovascular markings Some collapse within the lesion was frequent but occasionally it could be detected only by most careful film inspection Some shift of position of the interlobar fissures and crowding of the bronchovascular pattern were often the only signs of collapse

The features in these 500 cases correspond to those of atypical primary pneumonia These and most cases of atypical pneumonia are attributed to aspiration of products from the upper respiratory infection The following points are advanced in favor of this concept (1) The cases followed an upper respiratory infection (2) All lesions appeared in dependent bronchopulmonary segments or subsegments (3) Symptoms often first arose after severe physical exercise during upper respiratory infection (4) Radiologic changes indistinguishable from those of primary atypical pneumonia have been seen in the surgical wards and would normally be termed postoperative aspiration pneumonia Two cases followed dental extraction with prolonged hemorrhage and upper respiratory infection was not present

[While the conclusions of this study are more sweeping than would be conceded by most clinicians emphasis on the frequency of aspirational pneumonias is correct Certainly it could be agreed that such a mechanism should be considered in atypical pneumonias —Ed]

Experimental Food Aspiration Pneumonia was studied by Thomas J Moran[7] (Univ of Pittsburgh)

METHOD —Common cooked foods were injected intratracheally in 1 cc doses into 60 healthy adult guinea pigs The foods were not mixed and only one type was injected into each animal Food was well ground suspended in isotonic sodium chloride solution and filtered through a single layer of gauze before injection Sterile technic and ether anesthesia were used at first but later injections were made without these precautions One animal died in 24 hours others

(7) A M A A ch P th 52 350 354 O tobe 1951

were killed by chloroform inhalation from a few minutes to 2 months later At least three blocks were elected from each lung and fixed in 4 per cent formaldehyde solution. Paraffin ections were stained with hematoxylin eosin

Gross changes were nonspecific and varied from edema and congestion to nodular bronchopneumonia In late stages small granulomatous or fibrotic nodules were noted In animals killed in one hour or less many microscopic food particles were found in bronchi and alveoli but definite pneumonia was not present Edema and congestion were often striking In 2 12 hours acute pneumonia developed (Figs 17 20) Giant cell formation was noted in a few cases as early as 12 hours after injection and in many cases an extensive giant cell reaction around food particles in 24-48 hours (Figs 21 24) After a week numerous large granulomatous areas were noted in many of which food particles were still intact in others they were partially degenerated or absent At one to two months the lungs contained extensive patchy granulomatous areas many of which contained no recognizable food particles Definite areas of fibrosis were noted after two months

In addition to local reactions around the food general pneumonic reaction developed in two to six hours sometimes being quite widespread Some of the pneumonic areas apparently disappeared whereas others formed extensive chronic granulomas

The similarity of known food particles in guinea pig lungs and material found in human lungs suggests that food particles may be commoner in routine sections of human pneumonias than is generally realized The absence of definitely recognizable food particles in fairly large pneumonic areas stresses the necessity of studying multiple sections from various areas when food aspiration pneumonia is suspected

[Aspiration of food has been discussed in the literature by pediatricians who have observed the effect in infants Aspiration occurs also in older persons particularly those whose protective reflexes are impaired. This article gives us a better understanding of the results—Ed.]

Aspiration of Gastric Contents Experimental Study is presented by J Robert Teabeaut II[8] (Harvard Med School) In rabbits aspiration of gastric contents caused pulmonary edema congestion hemorrhage de epithelization of bronchial

(8) Am. J Path 28 51 67 J F b 195



F g 21 (t p l ft) —Ea ly g ul m t e ct on arou d food w th f m t on of fo eign body g a t ll

F g 2 (t p right) —Ch g a l m how g l g f e g body gi t ll but n food a ly r c g hl food pa t l w e fou d t s d p i block

F g 23 (bottom l ft) —F t r c a l w pow ew

F g 24 (bottom r ght) —F b ot h gh pow w

(C te y f M T J A M A A h P th 52 350 354 October 1951)

response to the inanimate aspirated particles is expected to persist until adequate disposition of them is effected

Experimental Endogenous Lipoid Pneumonia is described by Paul Gross Jack H U Brown and Theodore F Hatch[9] (Pittsburgh) Fifty rats were exposed to air laden with antimony trioxide dust of 0 6 μ mean particle size Period of exposure averaged 25 hours/week and exposure was continued for 14½ months As controls 100 rats were exposed under identical conditions to dust containing only 1% antimony trioxide Animals were killed at regular intervals

No significant difference was noted in gross appearances of the lungs until about the ninth month when the experimental group showed scattered chalk white pleural foci about 2 mm in diameter With longer exposure mottling increased in intensity and became associated with uniformly distributed fine depressions suggestive of orange skin There were surprisingly few instances of grossly recognizable spontaneous pneumonia or bronchiectasis in the experimental group (9 deaths) the controls showed a higher incidence of pneumonia and bronchiectasis with 14 and 18 deaths from each

Early microscopic changes in the lungs of the experimental group consisted of proliferation swelling and desquamation of alveolar lining cells Metabolic disturbances in macrophages led to their fatty degeneration and necrosis Lipids derived from such cells were demonstrable as sudanophilic droplets and crystals The latter were soluble in fat solvents and gave a positive reaction for steroid (cholesterol?) It is these lipids from the disintegrated macrophages which cause varying degrees of pulmonary fibrosis Absence of fibrosis from lymph nodes which contained heavy deposits of antimony trioxide was considered evidence that this compound does not directly cause pulmonary fibrosis Similar pulmonary lesions though much less severe were produced in rats by intratracheal injections of finely divided antimony trioxide (75 125 mg) as aqueous suspensions

Possible clinical implications are (1) that other pneumoconioses may be associated with lipidic substances of endogenous origin and (2) that certain clinical lipoid pneu

(9) Am J P h 28 211 218 M Ap 395

mucosa and neutrophilic cellular response in the acute phase These changes were nonspecific After the initial response tissues reacted to the aspirated macroparticulate matter by granulomatous inflammation Occasionally pH of the aspirated material was below 2 4 and the continued reaction granulocytic A combination of these two types of cellular response may be present The enzymes in aspirated gastric content had little or no importance in pathogenesis of aspiration pneumonia or its complications The few pathogenic organisms present are not related causally to aspiration pneumonia but may be important in its complications

Pneumonia resulting from aspiration of gastric contents depended primarily on the physical and chemical properties of the aspirated macroparticles Regardless of composition of gastric content if its pH was lower than 2 4 aspiration produced pneumonia Complications such as abscesses bronchiectasis and so called pulmonary gangrene resulted primarily from bronchial obstruction by aspirated material or by the exudative reaction caused by it

Clinically the two important phases of aspiration pneumonia are the immediate reaction in which pulmonary edema or bronchial obstruction may jeopardize the patient s life and the delayed complications of chronic bronchial obstruction The acute reaction may be fatal steps to combat pulmonary edema which may be profound should be instituted Fluid and especially particulate matter should be removed as completely as possible from the respiratory tract In some cases this may establish an adequate airway If however the distress is not rapidly relieved regardless of the certainty regarding patency of the airway bronchoscopy should be done immediately After the acute phase continued efforts should be made to expel any macroparticles from the bronchial passage Such particulate matter usually does not completely obstruct the airway but the inflammatory exudate that it calls forth leads to obstructive bronchiolitis followed by atelectasis and more serious pulmonary disease Pathogenesis of aspiration pneumonia does not depend on bacteria and therefore antibiotics are not of primary therapeutic value although they are useful in preventing secondary infectious complications Regardless of administration of antibiotics the tissue

TUBERCULOSIS

Mechanism of Liquefaction of Tubercles Behavior of Endocellular Proteinases in Tubercles Developing in Lungs of Rabbits exposed to standardized aerosol suspensions of virulent bovine tubercle bacilli of the Ravenel strain was studied by Charles Weiss and Marial L Boyar Manstein[2] (Jewish Hosp of Philadelphia) By killing the animals at varying intervals after infection observations could be made at successive stages of tubercle development Rates of hydrolysis of benzoyl l arginine amidase and leucine amino peptidase were studied on material removed from the interior of liquefied tubercles from the centers of caseation and from the zones of inflammation which surround tubercles These data on proteinase activity were correlated with histologic findings on comparable specimens

Both substances showed greatly increased enzymatic activity in the inflammatory zones of the tubercles The lung areas intermediate between primary tubercles which contained only microscopic areas of cellular infiltration showed only moderate increase in the rate of enzymatic hydrolysis The rate of substrate cleavage was strikingly decreased in the zones of caseation becoming very low for the peptidase and reaching zero for the amidase

The findings suggest that the rate of proteinase action is proportional to the intensity of cellular infiltration that wherever there are intact cells there is proteinase action and that wherever the cells have undergone caseation or softening this action is decreased or absent This decreased proteinase activity may result not only from loss of certain enzymes and their activators but also from the presence of inhibitors

[The liquefaction of necrotic tuberculous lesions i one of the commonest factors in progressive d sease being largely respons ble for the bronchial d ssemination ob erved in pulmonary cases The mechanism of liquefaction has always been my teriou This study is an approach to the explanation —Ed]

Study of Relation of Nutrition to Development of Tuberculosis Influence of Ascorbic Acid and Vitamin A For 1 month to 5 years (average 1 5 years) Horace R Getz

(2) Am R T b 63 694 705 J 1951

monias not now fully explained may be related to endogenous lipids

[This conception of a peculiar type of pneumonia which often leads to fibrosis may help explain cases previously reported in the literature Pathologists report a common finding of fat laden cells in various types of pneumonia of long duration —Ed]

Pulmonary Fibrosis Secondary to Pneumonia Stewart H Auerbach Oscar M Mims and Ernest W Goodpasture[1] (V A Hosp Nashville Tenn) collected and examined sections obtained at 307 complete autopsies performed on adults in 1946 50 (group 1) Primary causes of death varied widely but there was an unusually large proportion of malignant neoplastic diseases The lung sections were examined microscopically for fibrosis It was attempted to confine observations to pulmonary fibrosis secondary to pneumonia presumptively caused by exogenous infectious agents in which resolution would be the expected outcome With the idea that increased use of antibiotics might have affected incidence of organization 100 autopsies done in 1940 (group 2) and 100 done in 1930 (group 3) were similarly reviewed

Organization in this restricted sense was seen in sections from 38 of the group 1 patients or somewhat more than 12% In group 2 seven showed organization in group 3 five These relatively small groups do not permit generalization or deduction that organization is increasing but the suggestion is made to stimulate similar comparisons

Microscopic characteristics varied but two fairly distinctive patterns were recognized one in which intra alveolar organization was predominant and one in which interstitial fibrosis was predominant Although all cases fell into one of these patterns because of the major type of lesion there were many instances of overlapping and characteristics of both patterns could be seen in the same lung Primary intra alveolar organization was seen in 16 patients in group 1 in 1 in group 2 and in 3 in group 3 Fibroblastic invasion of the exudate with ultimate formation of strands of fibrous tissue in the alveoli and bronchioles was characteristic Anatomically these lesions were often found in a peribronchial or subpleural position but if large resulted in a fleshy elast ~ carnified lung

(1) Am J Path 28 69 87 Jan F b 195

83% and the study may represent a disproportionately high percentage at the lower socioeconomic levels (3) the diabetics surveyed were the survivors of a group whose characteristics remain unknown e g diabetics in whom tuberculosis developed promptly after coma might have died so rapidly that those patients who had a history of coma were not representative

The diabetics under 40 had a prevalence of active tuberculosis of 5 3% as contrasted with 1 7% for those over 40 Total tuberculosis prevalence did not always bear such an apparently direct relation probably because fibrocalcific and strandlike le ions may antedate the diabetes The diabetics under 40 had a tuberculosis prevalence of 5% with diabetes of less than 10 years duration whereas i was 17% when diabetes had been present for over 10 years This relation was not noted in persons over 40 The situation was similar when active tuberculosis only was considered

It was surprising to note a higher prevalence of tuberculosis (9 2%) in the 743 patients who were *not taking* insulin than in any other group This was due largely to presence of diabetics over 40 but other factor may have been involved There was a direct correlation however between increasing severity of diabetes and increasing prevalence of active tuberculosis this was increased from about 1 5% for those who received no insulin or no more than 40 units to 5 3% for those taking over 40 units each day The effect of control a measured by five recent blood sugar analyses was difficult to evaluate In diabetics receiving over 40 units of insulin there was a greatly in reased prevalence of active tuberculosis among those with good control possibly due to meticulous efforts to maintain normal blood sugar values in the presence of symptoms actually due to tuberculosis On the other hand five recent blood sugar values may not necessarily reflect status of the diabetes at the time of onset of tuberculosis No correlation was found between history of coma and active tuberculosis Since coma is evidence of uncontrolled diabetes the lack of relationship between history of coma and active tuberculosis tends to increase the difficulty of evaluating the role of control in diabetic predisposition to tuberculosis Another unexpected observation was that there

Esmond R Long and Howard J Henderson[3] (Univ of Pennsylvania) followed 1 100 men (83% Negroes) aged 20-45 who had no x ray evidence of pulmonary tuberculosis at first examination Periodic roentgen examinations clinical studies and serial nutritional assays were made (persistence of nutritional pattern insured suitability for this study) Nutritional assay included measurement of blood concentration of hemoglobin plasma carotene vitamins A and C total serum protein and serum albumin globulin calcium phosphorus and phosphatase Clinical examination in addition to specific tests for tuberculosis included calculation of per cent standard weight and in many cases measurement of bone density

Of 28 persons with roentgen evidence of tuberculosis during the seven year investigation 16 had active disease fatal in 4 Lesions in 12 appeared inactive when first detected but in 4 they fluctuated in a visibly favorable way indicating recent activity Nutritional assays in 28 gave values evenly distributed through the ranges of values for all 1 100 with respect to all blood elements studied except vitamins A and C All cases of clearly active disease appeared in persons with markedly substandard values for vitamins A and C before development of tuberculosis An inverse relation thus was evident between development of tuberculosis and blood concentration of these vitamins No correlation was found in development of tuberculosis and deviation from standard weight or bone density

[Although long recognized that nutritional deficiencies play a role in the development of tuberculosis the specific factors have not been entirely clear This is a significant contribution —Ed]

Tuberculosis among Diabetics Philadelphia Survey Katharine R Boucot Edward S Dillon David A Cooper Paul Meier and Russell Richardson[4] found that prevalence of tuberculosis among 3 106 diabetic patients in 1946 was 8 4% Prevalence in a group of apparently healthy industrial workers adjusted for age race and sex was 4 3% Seventy per cent were females and 27 7% nonwhites Certain fundamental limitations of the survey must be recognized (1) only known diabetics were studied (2) proportion of clinic patients was

(3) Am Rev T ber 64 381 392 Octobe 1951
(4) Ib d 65 1 50 Ja a y 195

The analogy to the presence or absence of active tuberculosis in man infected with tubercle bacilli is evident The inhaled bacilli multiplied only a short time in resistant rabbits and were usually rapidly and completely destroyed In susceptible rabbits they multiplied profusely for a much longer period and persisted in large numbers even months after inhalation In the most resistant rabbit destruction did not take place before some preliminary multiplication Native resistance is apparently merely a tendency for rapid development of ac

F g 5—L g f pt bl abb t (*A*) i f ta t bb t (*B*) 166 167 d y ft m lt ou h 1 t f b t 2 000 h m n typ tub l b ll L g f pt bl bb t ta m tub l th f t t bb t f t m t b cul g os ly (Cou t y f L M B *t l* J E pe M d 95 119 134 F b 1 195)

quired resistance and native susceptibility a tendency to tardy or ineffective development of acquired resistance De velopment of acquired resistance against human tubercle bacilli was sufficiently rapid to affect the genesis of the initial gross primary pulmonary foci that resulted from inhalation of the bacilli The greater the genetic resistance the fewer are the initial primary foci Figure 25 shows the lungs of a resistant rabbit with no gross evidence of disease

With doses of inhaled bacilli ranging from 100 to about 2 000 the tuberculin reaction appeared more quickly in the resistant than in the susceptible animals With larger inhaled doses allergy still tended to develop more rapidly in the resistant animals but this was not always true Hemaggluti nins generated by this infection were of low titer in both

was no more tuberculosis among those with history of gangrene amputation boils or carbuncles than in the diabetics without such histories

As in nondiabetics prevalence of tuberculosis was twice as high among those below standard weight as among those over it This effect was independent of age, severity and impression of activity Since accepted diabetic therapy emphasizes the desirability of reducing diabetics to or slightly below standard weight this should be kept in mind

The difference between the 261 tuberculous diabetics and a nondiabetic comparison tuberculous group adjusted for age race and sex could in general be accounted for by the fact that the diabetics had a higher percentage of active tuberculosis 31% as contrasted with 11% in the comparison *group There was no appreciable difference between the* groups in the amount of active tuberculosis in the lower two thirds of the lung fields However over half of both groups had active tuberculosis confined to the lower two thirds which suggests that age rather than diabetes may be the factor responsible for the impression that diabetics have more basal tuberculosis

***Response of Genetically Resistant and Susceptible Rabbits* to Quantitative Inhalation of Human Type Tubercle Bacilli and Nature of Resistance to Tuberculosis** Rarely if ever is a primary bovine tubercle infection completely overcome even by the most resistant rabbit On the other hand, in most human beings infected with tubercle bacilli the disease is completely arrested To understand the nature of human resistance to tuberculosis a disease must be produced in animals which is rarely fatal Primary pulmonary tuberculosis in unselected rabbits induced by quantitative inhalation of human type tubercle bacilli may retrogress or progress Max B Lurie Samuel Abramson and A G Heppleston[5] (Univ of Pennsylvania) therefore had inbred rabbits of resistant and susceptible strains inhale for a known time an aerosol containing a known number of bacillary units of viable virulent human type tubercle bacilli (H37Rv)

No tuberculosis was seen in the lungs of the resistant animals as a rule several months after infection whereas susceptible rabbits had variable and often extensive disease

(5) J Exper Med 95 119 134 Feb 1 1952

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F g 25—Lung f sc pt bl bb t (*A*) nd f ta t abl t (*B*) 166 167 day fter m lt ou h l t f about 2 000 h m type t be l ba ll Lu g f pt bl bb t ta n m s tube l th f t nt bh t f e from t be culos g os ly (Cou t y f Lu M B et l J E pe Med 95 119 134 F b 1 1952)

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groups Nevertheless antibody response tended to be more rapid in the resistant rabbits Whatever the cause of the more rapid destruction of tubercle bacilli in the resistant animal the resulting more rapid release of the contained antigens enhances development of allergic sensitivity and antibodies in these animals

It is suggested that variations in genetic resistance to inhaled human type tubercle bacilli may affect the prevalence of alveolar phagocytes capable of acquiring adequate resistance to the growth of the bacilli in their cytoplasm Prevalence of such cells is subject to hormonal and immunologic influences

[The study of native resistance and its operation is one of the most fascinating problems in tuberculosis Most workers have a growing belief that genetic and constitutional factors are highly significant This group of workers has made extremely important contributions —Ed]

Is There a Specific Personality in Tuberculous Patients? Edwin L Demuth[6] (White Plains N Y) contends that no specific personality pattern characterizes pulmonary tuberculosis patients Histories of five tuberculous and five non tuberculous psychiatric patients are reported in pairs and whereas the psychodynamics vary widely mechanism examples for each are found in both categories Both patients of one pair reported illustrated the obsessive compulsive and strong masochistic traits which resulted in depressed withdrawn shy passive behavior and both were so repressed that therapy was slow and painful yet much desired The second pair were immature dependent passive persons who refused to face reality or make decisions Unhappy parental and marital situations applied to both One escaped by excessive social activity which undoubtedly aggravated the tuberculosis the other by chronic whining complaining and evasion of her responsibilities Each projected her inadequacies onto others The former accepted psychotherapy with some benefit the latter rejected it The third pair were young men under constant tension from trying to meet unnecessarily strict parental demands Both had suppressed feelings of inferiority The tuberculous patient improved with streptomycin therapy and learned to socialize and to assert himself The other asserted himself by early marriage and learned to meet frustrations under psychotherapy *The fourth and fifth pairs all*

(6) A M A Arch Neurol & Psychiat 66 30 37 July 1951

illustrated strong domination and rejection by parents with resultant withdrawal from social contacts When tension be came excessive tuberculosis developed in one patient and drug addiction in another

Therapy was flexible and depended on the needs of the patient and time available Tuberculous patients of the 230 bed sanatorium studied had the services of a consultant psychiatrist one day a week and one full time clinical psy chologist and two trained social workers The number of in terviews ranged from 2 to 80 according to need There was no opportunity for intensive deep therapy yet nearly all patients acquired better insight and benefited from the psy chiatric service Results indicate the value of psychotherapy as an adjunct to pulmonary tuberculosis therapy

[Although the influence of emotional and psychologi factors on the course of a chronic disease like tuberculosis is generally recognized it has been difficult to identify specific patterns This article seems to represent a sensible approach — Ed]

Chemotherapy of Tuberculosis in Man Present Status A progress report of the study of 10 000 cases by the Veterans Administration Army and Navy presented by the Veterans Administration Committee on Streptomycin [7] re emphasizes the fact that streptomycin does not cure tuberculosis especially the pulmonary form Attempts have been made to extract the greatest possible benefit from the drugs at hand by over coming their disadvantages and using them in combination with bed rest and appropriate surgical procedures

Signs of renal irritation skin eruptions and fever appear occasionally in patients and allergic phenomena may develop in nurses who handle streptomycin and dihydrostreptomycin but both drugs are relatively nontoxic except for their action on the vestibular and auditory apparatus Vertigo occurred sometimes to an incapacitating extent in 80% of 671 patients receiving 2 Gm streptomycin daily for 120 days (regimen 1) Shortening therapy to 60 days reduced incidence to 63% but reduction in dosage was even more successful Vertigo appeared in only 8% of 1 006 patients receiving single daily injections of 1 Gm in 5 8% of 137 patients with 0 5 Gm /day and in 3 4% of 383 patients with 1 Gm twice a week Each of the three regimens was continued 120 days and in only two instances was vertigo described as severe or incapacitat

(7) J A M A 147 253 258 S pt 15 1951

ing These reductions in dosage were accomplished without detectable loss of therapeutic efficacy This statement is made with reservations only for the 0 5 Gm /day regimen At the lower dosage level the difference between streptomycin and *dihydrostreptomycin was relatively slight (8% as opposed to 3%)* After study of 800 cases the advantage in therapeutic efficacy seemed to favor use of streptomycin and dihydro streptomycin was discontinued Dihydrostreptomycin was more prone to produce deafness which can occur even at a dosage of 1 Gm /day if treatment is continued more than four months

Reducing duration of regimen 1 did not provide a satis factory solution to the problem of resistant strains There fore two other procedures were investigated concomitant use of para aminosalicylic acid (PAS) with streptomycin (regimen 2) and use of 1 Gm streptomycin twice a week (regimen 3) rather than daily Of 224 patients treated with the combined regimen only 31% (instead of 82% in tho e treated with streptomycin alone) of cultures which continued to be positive after 120 days of therapy were resistant to 10 μ/cc or more of streptomycin Decreasing frequency of injections to twice a week also met with some measure of success Resistant bacilli appeared more slowly and after 120 days of therapy 67% (rather than 82%) of 118 positive cultures were resistant by the same criteria With combined intermittent therapy (1 Gm streptomycin twice weekly plus 12 Gm PAS daily given concurrently) resistance among positive cultures decreased to 17% after 120 days of therapy Since tubercle bacilli have been rendered streptomycin resist ant in so many patients and since this resistance is relatively permanent it is surprising that so few other patients seem to *have been infected by them This matter does not seem to* pose the serious public health problem envisaged earlier Increasingly cases are being reported in which some months or even years after cessation of streptomycin therapy and development of resistant bacilli sensitive cultures have been obtained This seems likely no longer to be a laboratory error but an expression of the heterogeneity of the bacillary population with regard to streptomycin

Advances made in overcoming the factors of toxicity of and bacterial resistance to streptomycin would have been

useless if accomplished at the expense of therapeutic efficacy Actually improvement rate was satisfactorily maintained (table) The encouraging difference in incidence of sputum conversion is presumably due to the concomitant collapse therapy permitted with regimens 2 and 3 Follow up data describing the effects of eight regimens in 813 cases during

THERAPEUTIC EFFICACY OF THREE REGIMENS IN PULMONARY TUBERCULOSIS

R U	R M 1		R M 2		R M N 3	
	C	%	C	%	C	%
Radiologic improvement						
Moderate or pronounced	248	66	209	48	139	46
Slight	64	17	131	30	94	31
All degrees	312	83	340	78	233	77
Total cases observed	375	100	436	100	303	100
Sputum conversions		32		59		56
Total cases observed	120		316		209	

the preceding year howed that regimens enduring for 120 days seemed superior to those of 90 days On the other hand little or no difference in therapeutic efficacy could be demon strated by substitution of (1) interrupted (twice weekly) for daily therapy or (2) dihydrostreptomycin for streptomycin in equivalent (1 Gm daily) dosage

In study of extrapulmonary tuberculosis the need of a two year period for follow up and use of a wide variety of regimens made further evaluation difficult although combined PAS and streptomycin may have further increased the sur vival rate of patients with meningeal or miliary tuberculosis No final recommendations were made on intrathecal admin istration of tuberculin because of its possible dangers

In 123 patients with genitourinary tuberculosis observed more than one year since completion of a first course of chemo therapy and 100 for more than two years outstanding observa tion was that conversion of urine from positive to negative had withstood the passing of time In the renal lesions there was a drop from 53% immediately after treatment to 47% more than two years later in genital lesions from 78 to 70% and in combined lesions from 50 to 33% Daily dosage of 2 Gm streptomycin seemed slightly more effective than 1 Gm and the 42 day regimen definitely less effective than the 120 day Data on the combined regimens were insufficient to determine whether any advantage had been gained by addition of PAS

In thoracic surgery increase in complications after excision and decortication noted with preoperative streptomycin treatment was attributed partly to widening of indications for surgery and emergence of resistance Results were somewhat inferior even in the absence of resistant strains before surgery No satisfactory clinical results have been obtained with any other antibiotics or drugs

↓ During the past year discovery of new drugs which have an inhibitory effect on the tubercle bacillus has raised many problems requiring prolonged study and evaluation Early in 1952 a barrage of newspaper publicity relating to the announcement of the therapeutic effects of isonicotinic acid hydrazide conveyed many erroneous impressions and misstatements of facts It was implied that this drug would kill bacilli specifically in the human being would revolutionize treatment and remove the necessity of providing hospital beds for many patients The initial confusion rapidly subsided and although knowledge of the new drug is still inadequate some ound observations have been made No evidence of a bactericidal effect in man has been reported nevertheless the drug is active therapeutically and this activity is important because therapeutic doses have not produced evidence of serious toxicity Initial symptomatic effects are striking just as they have been with a number of antibiotics but the more profound effects on the lesions till require study The action may not be as potent as that of streptomycin Early development of drug resistance by the bacillus has been observed and this will be a hindrance

In addition to this drug which has the virtue of relative cheapness and therapeutic effect when given by mouth viomycin aldinamide and several newly synthesized chemicals have received continued study Now that a number of specific agents are becoming availabl an important problem will be to learn to use them properly in sequence and in various combinations Combined therapy with streptomycin and para amino salicylic acid has been appli[ed] wid[e]ly with demonstration that manifestations of drug resistance may be greatly delayed Others have combined streptomycin with terramycin and with amithiozone with similar results In all probability variou combinations may be used in sequence thus maintaining a bacteriostatic effect for many months or several years This is obviously highly significant for the tuberculous patient In some lesion resected after prolonged combined therapy tubercle bacilli are found on staining but they sometimes fail to grow in the usual culture mediums or to reproduc the disease in guinea pigs It is still a moot question whether the bacillus has died or has merely changed its characteristics of growth —Ed

Antituberculous Properties of Hydrazines of Isonicotinic Acid (Rimifon Marsilid) William Steenken Jr and Emanuel Wolinsky[8] (Trudeau Found) report preliminary observations on the antituberculous activity of these drugs based on results in the test tube and in infected guinea pigs and rabbits Both drugs had tuberculostatic and tuberculocidal action in

(8) Am Re T ber 65 365 375 Apr l 1952

vitro The parent compound rimifon (isonicotinic acid hydra zide) showed greater activity than marsilid (1 isonicotinyl 2 isopropyl hydrazine) Neither drug was more than slightly affected by presence of serum in the medium Tubercle bacilli could not readily be made highly resistant to these drugs by serial passage in vitro but this does not necessarily mean that resistance will not appear in cultures from patients treated with the drugs for prolonged periods

Guinea pigs infected subcutaneously with virulent human tubercle bacilli and treated 21 days later with marsilid re vealed little evidence of tuberculosis grossly when killed 73 days after infection Initial dose was 20 mg of the dihydro chloride salt intramuscularly once daily but after 26 days 35 mg and later only 25 mg daily were given orally After 30 days the tuberculin skin reactions which had been highly positive at the beginning of therapy were altered to negative or doubtful reactions Guinea pigs infected intracerebrally with virulent human tubercle bacilli but not treated died within 25 days whereas those treated with marsilid remained well during 60 days of therapy

Rabbits treated with marsilid for 71 days after infection intravenously with highly virulent bovine tubercle bacilli remained well and had no miliary pulmonary lesions on x ray whereas controls died of advanced miliary tuberculosis within 30 days of infection The surviving rabbits however re lapsed within 10 weeks after treatment was stopped

The dihydrochloride salt of marsilid gave highly acid aqueous solutions which when injected intramuscularly pro duced local necrosis and induration When the solutions were neutralized however or when the drug in the form of the free base was used local reactions were minimal Administra tion of 20 mg twice daily intramuscularly to guinea pigs (70 mg/kg/day) for eight days produced steady weight loss and 20 mg once daily (35 mg/kg/day) produced weight loss and occasional death after three weeks A regimen of 10 mg twice daily (about 35 mg/kg/day) was tolerated well for 60 days Rimifon in doses up to 35 mg/kg/day was tolerated well for six weeks Orally marsilid and rimifon were tolerated well by guinea pigs in single daily doses up to 40 mg/kg

On Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in Experimental Tuberculosis Infection of Mice E Grunberg B Leiwant, I L D'Ascensio and R J Schnitzer[9] (Nutley N J) infected mice with Mycobacterium tuberculosis H37Rv by intravenous or intranasal route and treated them with various agents in medicated diets (except for streptomycin given intramuscularly) for 21 days The success or failure of this treatment was evaluated after 21 more days without any drug Under these conditions daily streptomycin (50 mg/kg) PAS (2 5 Gm/kg) tibione® (2 5 Gm kg) nicotinaldehyde thiosemicarbazone (500 mg/kg) and isonicotinaldehyde thiosemicarbazone (500 mg/kg) given in doses high enough to protect the mice for the duration of treatment did not prevent extensive lung involvement after therapy was stopped

Rimifon 50 mg/kg daily in medicated diet and marsilid 25 mg/kg protected about 50% of the animals against intravenous infection and made them completely free from lesions Although lower doses did not protect a significant number of animals these drugs seemed to exert a pronounced effect on the life span and severity of pulmonary lesions After 42 days 81 7% of the untreated controls had died In animals given 12 5 250 0 mg/kg rimifon death rate was negligible With marsilid mortality was low with even the lowest doses (6 25 mg/kg) Pulmonary involvement was in good agreement with both protection rate and survival time Both compounds still appeared notably active in the dosage range of 25 0 mg/kg

With intranasal infection the over all picture of the protective effects of the two compounds was similar Intranasal infection is usually milder although more resistant to treatment Tibione® nicotinaldehyde thiosemicarbazone and isonicotinaldehyde thiosemicarbazone which suppressed the lesions for duration of treatment were ineffective after treatment was stopped PAS was completely inactive Rimifon and marsilid on the other hand protected most animals given doses as low as 12 5 mg/kg With intranasal infection parenteral treatment with rimifon and marsilid only once daily subcutaneously was as effective as administration by diet which results in more continuous medication Given

(9) Dis Chest 21 369 377 Ap 1 1952

subcutaneously for 21 days 50 0 mg /kg rimifon or marsilid kept 90 100% of the animals alive and free from lesions after 42 days The same dose of streptomycin was entirely inactive

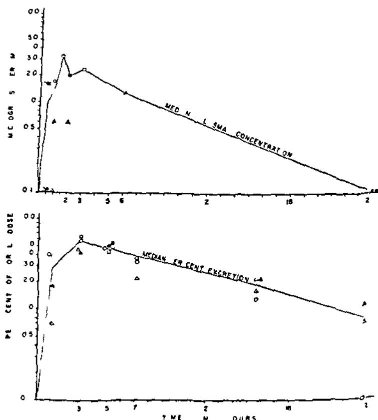
Absorption Distribution Excretion and Short Term Toxicity of Isonicotinic Acid Hydrazide (Nydrazid) in Man were studied by DuMont F Elmendorf Jr William U Cawthon Carl Muschenheim and Walsh McDermott[1] (Cornell Univ) A single oral dose of 3 mg nydrazid/kg body weight was administered to each of six adults with normal renal function The drug was absorbed promptly and maximal plasma concentrations (1 3 3 4 μg /ml) were attained 1 6 hours after ingestion (Fig 26) drug concentrations at or above the minimal concentration detectable (0 40 μg /ml) persisted in the plasma for 6 24 hours Plasma concentrations attained after a morning dose of 1 5 mg /kg were determined in five patients receiving this dose twice daily for a minimum of one week Maximal concentrations among the individual patients ranged between 0 60 and 1 48 μg /ml and the drug could be detected in the plasma for three to seven hours after administration In seven patients receiving a total of 3 mg /kg daily (in two doses) weekly determinations of plasma concentrations were made about three hours after the morning dose There was no evidence of accumulation of the drug on long continued administration

Figure 27 shows the percentage of the 3 mg /kg dose excreted per hour by the six patients Study of concentrations of drug in plasma and urine during the same 24 hour period showed that the individual patients excreted between 47 8 and 70 7% of the dose administered During the 24th hour after administration of the drug between 0 03 and 1 1% of the dose was excreted Although it was not possible to demonstrate the drug in the plasma at the 24th hour the amounts excreted in the urine presumably reflect the presence of substantial though undetectable quantities in plasma

Transfer of nydrazid into the cerebrospinal fluid after oral administration was studied in four adults and five children Three presented no evidence of meningeal infection A fourth had been treated for tuberculous meningitis but had had no clinical or cerebrospinal fluid evidence of active menin

(1) Am R v T b 65 429 442 Ap l 1952

geal infection for three months The other five had active tuberculous *meningitis Doses of 1 5 3 5 mg /kg were given Appreciable concentrations of the drug were present in the* cerebrospinal fluid of all patients Comparison of the concen



F g 26 (top) —Pla ma co c nt at o s bj ct g en 3 mg /kg n d ar l
F g 27 (bo t m) —E c t f drug n f sam x pat t
(C rt y f Elm ndo f D F Jr f l Am R T b 65 4 9 442 Ap l 1952)

trations in patients with and without *meningitis* was not possible because of difference in dosages of the two groups Without regard to time of withdrawal of the cerebrospinal fluid (3¼-4 hours after last oral dose) concentrations in the five patients with active meningitis (1 77-4 10 μg /ml) were substantially higher than the concentration (0 06 μg /ml) which

completely inhibits the H37Rv strain of Mycobacterium tuberculosis for 14 days in vitro Repeated examination of the cerebrospinal fluid of the five patients with active meningitis at weekly intervals showed no significant change when the fluid was obtained at about the same time after the last oral dose as in the preceding weeks

Distribution of nydrazid into the pleural cavity was studied in one patient with tuberculous empyema who had not previously received the drug Two hours after ingestion of a sin le dose of 2 mg/kg concentration of 0 0-0 4 μg/ml was found in the pleural exudate

No evidence of potentially serious toxicity was encountered In one patient 15% eosinophilia was noted but this disappeared within three days despite continuation of the drug Serial tests on seven patients given 3 mg/kg daily for a minimum of four weeks revealed no disturbances of renal or hepatic function No evidence of excitation of the central nervous system was noted Vertigo and dizziness were uniformly denied

Hydrazine Derivatives of Isonicotinic Acid (Rimifon Marsilid) in Treatment of Active Progressive Caseous Pneumonic Tuberculosis Preliminary Report on 44 patients with acute active progressive bilateral caseous pneumonic tuberculosis is presented by Edward H Robitzek and Irving J Selikoff (Sea View Hosp Staten Island N Y) Only patients with extensive disease were selected the so called hopeless case many were close to terminal status Each patient during average pretherapy observation of 5 2 months/patient had either stationary or progressive disease In all sputum was persistently positive for Mycobacterium tuberculosis and temperature was continuously elevated (100 105 F) for one to five months All had lost weight and failed to gain appreciably despite other forms of therapy Initially the drugs were given in doses of 2 mg/kg body weight daily but doses were finally elevated to 4 mg rimifon/kg and 10 mg marsilid/kg All other therapy was discontinued while the drugs were given

In 42 of the 44 patients temperature subsided promptly and sometimes precipitously Defervescence was sustained in all after the initial fall except during transient upper respira

( ) Am R T b 65 40 4 8 Ap 1 195

TEMPERATURE

105 104 103 102 101 100 99 98 97

DAYS BEFORE THERAPY

DAY OF THERAPY

4572



F g 28 (top) —Temp r tur c how g p t tly el ted t mper tu wh ch a h d mal o t th d y f th rapy
F g 29 (b tt m l ft) —N 7 1951 La g y t m of c it th ghout left l g nd ud t e l n n ght
F g 30 (b tt m r ght) —J 7 195 Ca t es g atly d ed t ally l ed (Cou t y f Rob t ek E H nd Sel k ff I J Am. R T be 65 40 4 8 Ap l 195)

tory infections in six Weight gains were most spectacular (average 19 7 lb in 8 8 weeks) Abnormal accumulations of body fluids were not found Appetites were remarkable In all patients energy and sense of well being were greatly improved

and apathy and drowsiness completely relieved in the second week Relief from cough and expectoration was noted with regularity during the second week of therapy In 38 patients sputum bacillary contents were reduced and in 8 examinations for acid fast bacilli on stained smears (including gastric washings) gave repeatedly negative results Roentgen examination revealed reduction of cavity size in 17 patients and apparent diminution of exudate in 5

Therapeutic effects of rimifon after four weeks at 4 mg /kg daily were roughly equivalent to those of the isopropyl derivative marsilid at the same dosage Incidence of early side reactions was moderately higher with marsilid at comparable dosages although on the basis of preliminary animal studies rimifon may have a higher potential delayed toxicity Side effects included dizziness constipation twitching of extremities hyper reflexia insomnia drowsiness headache weakness of the legs delayed urinary stream drynes of the mouth and dyspnea

Negro woman 24 first had symptoms of pulmonary tuberculosis in 1948 Status became critical Weight decreased from 125 to 80 lb Severe anorexia lethargy weakness moderate cough and expectoration were present There was persistent diarrhea possibly due to tuberculous enteritis There were 3+ pitting edema of the extremities and 2+ albuminuria possibly due to amyloidosis Sputum was highly positive for acid fast bacilli on every examination

On Nov 24 1951 marsilid therapy was begun 4 mg /kg daily Temperature began to descend (Fig 28) appetite became ravenous diarrhea subsided completely within two weeks and edema disappeared during the first week There was a remarkable gain in well being After four weeks cough and expectoration had almost completely disappeared Rapid weight gain was noted (37 lb after eight weeks) Two sputum examinations in the first two weeks were positive for acid fast bacilli the next week a smear was negative and five subsequent examinations were negative including those of samples obtained by gastric aspiration On Jan 7 1952 a roentgenogram showed great improvement over the pretherapy picture The multiple cavities in the left lung were all much smaller (Figs 29 and 30)

Antituberculous Action of Nicotylamides B Fust and A Studer[3] (Basel) injected standard doses of tubercle bacilli intravenously into mice The next day oral or subcutaneous administration of nicotylamide preparations was begun The

(3) H I t m d ta 18 449 455 Octobe 1951

animals were killed and examined 3½ weeks later Lungs were examined grossly and microscopically Morbidity indexes were calculated by multiplying grade of the gross lesions (grades 1-4) by percentage of animals with such lesions and adding these Indexes were also calculated for micro scopic lesions

Minimal effective oral dose of nicotylamide was 1 Gm/kg body weight Lower doses were practically inactive Sub cutaneous administration was two to three times as effective as oral

Absolute morbidity index for the lungs (corrected for animals dying during the experiment) was 80 for nicotinic acid (300 mice) 153 for PAS (110 mice) 156 for para acetamino benzaldehyde thiosemicarbazone (100 mice) 173 for streptomycin (100 mice) and 299 for controls (609 mice) Morbidity indexes for microscopic lesions in the lungs and liver showed the same trends although liver lesions were affected less by treatment The liver is therefore recom mended as a test organ for evaluation of antituberculous drugs

Nisin in Experimental Tuberculosis E M Bavin A S Beach R Falconer and Rosa Friedmann[4] investigated the antibiotic nisin produced by a strain of Streptococcus lactis but were unable to confirm early hopes for the drug Although it proved effective against many gram positive organisms including Mycobacterium tuberculosis its activity on a weight basis was less than that of penicillin against gram positive organisms and less than that of streptomycin against the tubercle bacillus Its activity appeared to be reduced by serum and its effectiveness in vivo was less than was antici pated from in vitro experiments Doses near LD_{50} were in jected subcutaneously intravenously and intraperitoneally into guinea pigs and blood drawn two hours later was assayed for activity against virulent tuberculosis bacilli With one exception and regardless of route the blood allowed the organisms to grow at the same rate as did the blood of controls These and similar experiments showed that it is difficult to maintain nontoxic blood nisin levels high enough to suppress the growth of tubercle bacilli

The best nisin producing organism so far isolated yields

(4) Lancet 1 127 129 J 19 1952

only about a thirtieth of the quantity of therapeutic substance obtained with the producers of penicillin and streptomycin thus making the cost of nisin appreciably higher than that of the other two antibiotics Results indicate that nisin is most unlikely to find a place in therapeutics

Specific Treatment of Children with Tuberculosis Edith M Lincoln and Virginia N Wilking[5] (New York Univ) review treatment in 172 children All tuberculous children were divided into three groups in which chemotherapy was (1) indicated (2) elective or (3) contraindicated Streptomycin was considered mandatory in meningitis protracted hematogenous tuberculosis generalized miliary tuberculosis locally progressive primary infection and reinfection pulmonary tuberculosis Specific treatment was elective in tuberculous otitis and cervical adenitis endobronchial disease econdary to primary tuberculosis tuberculous laryngitis bone and joint tuberculosis and to cover surgical procedures In uncomplicated primary tuberculosis and minimal chronic pulmonary tuberculosis chemotherapy was considered contraindicated

TABLE 1—Treatment of Meningitis and Miliary Tuberculosis

A NT	Ro T	Dos	
		M l y T b	M g t
Streptomycin	Intramuscular	1 Gm. daily for 4 mo	1 Gm daily for 6 mo
Streptomycin	Intrathecal	——	100-50 mg for 40 or more injections
Thiazolsulfone	Oral	Increa ed from 0 5 Gm daily until blood level ı 1 3 mg /100 cc range 0 25 8 Gm daily every 6 hr continued 2 3 yr	

Table 1 shows the general scheme of treatment for acute meningitis and miliary tuberculosis In meningitis intrathecal therapy was discontinued after 40 injections only if cerebrospinal fluid sugar level had been above 40 mg /100 cc for one week the base line levels of cells and protein were not rising and the clinical condition was satisfactory Frequent lumbar taps immediately after completion of intrathecal therapy were followed by weekly lumbar taps which were continued for at least two months after completion of intramuscular streptomycin therapy Relapse of meningitis after completion of intramuscular therapy was treated in three patients by repeating the full course of intrathecal and

(5) A M A Am J D Child 8 655 665 D mb 1951

intramuscular therapy Three patients who had a recrudescence of meningitis while still receiving streptomycin intramuscularly received a further course of streptomycin intrathecally

In patients with both acute miliary tuberculosis and meningitis on hospitalization treatment was that for meningitis alone Patients in whom meningitis developed in the course of miliary tuberculosis were treated for six months from the date of diagnosis of meningitis

Therapy for protracted hematogenous tuberculosis pro-

TABLE 2—TREATMENT OF OTHER FORMS OF TUBERCULOSIS (OF LONG DURATION)

Agent	Route	Dosage	
		Protracted Hematogenous Tuberculosis	Progressive Primary, Chronic Pulmonary Tuberculosis
Streptomycin	Intramuscular	On wt basis for 2-4 mo	On wt basis daily for 2 4 mo or 0 5 1 Gm twice weekly indefinitely
Thiazolsulfone	Oral	Increase from 0 5 Gm daily until blood level is 1 3 mg/100 cc cont for 1 yr	—
Para aminosalicylic acid	Oral	—	0 5 Gm/kg daily

TABLE 3—DOSE OF STREPTOMYCIN ON WEIGHT BASIS

Wt of Patient Lb	Daily Dose Gm
Less than 10	0 3
10 19	0 4
20 39	0 5
40 59	0 6
60 89	0 75
90 or over	1 0

gressive primary tuberculosis and chronic pulmonary tuberculosis is outlined in Tables 2 and 3

Of 63 patients with other forms of tuberculosis all but six received streptomycin In four patients with tuberculous cervical adenitis treatment consisted of incision and drainage and local instillation of streptococcic enzymes Two with endobronchial disease received only PAS Streptomycin was given as the sole chemotherapeutic agent only when the total period did not exceed three weeks as in treatment of laryngitis or when it was used as a precautionary measure in

surgery Otherwise streptomycin was given in combination with PAS or thiazolsulfone Streptomycin was given according to the patient s weight (Table 3) thiazolsulfone and PAS as for other forms of tuberculosis Duration of combined therapy was six weeks to three months

In the two years before use of streptomycin death rate in the children s tuberculosis ward from complications of primary tuberculosis was 18% Since introduction of streptomycin the death rate in primary tuberculosis was under 3% Except for one due directly to miliary tuberculosis all deaths from primary tuberculosis were due to meningitis Three of 21 patients with early meningitis 2 of 8 with moderately advanced and 6 of 10 with late meningitis died Results in meningitis seem to depend partly on the stage of meningitis and to a less extent on the age of the child when meningitis is first diagnosed Meningitis patients who survived three months after streptomycin therapy was discontinued all remained well and there were no late relapses However seven were deaf three had residual hemiplegias and one had a footdrop Of 8 patients with protracted hematogenous tuberculosis 22 with progressive primary tuberculosis and 24 with chronic pulmonary tuberculosis all but 1 survived and many made remarkable clinical recoveries In some the change from a picture of emaciation and chronic illness to that of a healthy child was striking Residual cavitation or other evidence of residual disease however persisted on roentgenograms in some cases and surgery may be needed finally Except for one patient with exfoliative dermatitis no severe toxic reaction to intramuscular use of streptomycin was observed Almost all had loss of vestibular function but this was apparently reversible Deafness occurred only in patients treated intrathecally and was not reversible Toxic reactions to streptomycin intrathecally were never so severe as to require discontinuance of treatment Toxic reactions to thiazolsulfone were not troublesome PAS in proper dosage is remarkably well tolerated by children

Because of rapid healing of cutaneous sinuses overlying tuberculous bone disease and of tuberculous laryngitis and endobronchial disease associated with chronic pulmonary tuberculosis it is desirable to treat these forms with short courses of streptomycin even if the basic tuberculous disease

is not affected On the other hand routine use of streptomycin in tuberculous cervical adenitis is not advised In endo bronchial disease associated with primary tuberculosis the response was never definite and routine treatment of these patients was abandoned The risk of emergence of bacilli resistant to streptomycin must be constantly borne in mind in deciding on the use of streptomycin in complications of tuberculosis for which its value is unproved This is par ticularly true in primary tuberculosis in which the most compelling reason for withholding streptomycin is the lack of evidence that streptomycin is effective

[The striking change in mortality of tuberculous children is undoubt edly explained in recent years by the use of chemotherapy The prolonga tion of life will doubtless create other problems since some of these patients will pass over into chronic forms of tuberculosis —Ed]

Combined Intermittent Regimens in Treatment of Non miliary Pulmonary Tuberculosis Comparison of streptomycin every third day and para aminosalicylic acid daily with both agents given every third day in patients with proved moderate and far advanced pulmonary tuberculosis is presented by Frederic J Hughes Richard E Mardis William E Dye and Carl W Tempel[6] (Fitzsimons Army Hosp) In one group 95 patients received 1 or 2 Gm streptomycin every third day and 12 Gm PAS daily for 120 days 102 patients re ceived these doses of streptomycin and PAS every third day *for 120 days Six month follow up was completed on 81 and* 54 patients

Clinical response was about the same at 120 days Im provement continued during follow up in both groups but to slightly greater extent in those given PAS daily In both groups striking roentgen improvement observed after 120 days of therapy was usually maintained after 6 months In patients with cavities there was apparent closure in 20 5% on daily PAS and 26 2% on intermittent PAS during treat ment but 60 0 and 66 7% had cavity closure during the six month follow up largely because of operative procedures during this period On the two regimens 66 3 and 69 9% of patients had negative sputum after 120 days The proportion remained approximately the same at the six month evalu ation

None of the patients on daily PAS for 120 days yielded

(6) D s Chest 21 1 16 Ja a y 195

tubercle bacilli resistant to either streptomycin or PAS Of those on PAS every third day nine (29 0% of those with positive cultures) yielded organisms resistant to streptomycin after 120 days of treatment Bacterial resistance appeared in these patients only after an average of 106 days of drug therapy Comparison of patients whose sputum yielded resistant organisms to those whose sputum yielded sensitive organisms after treatment revealed no material difference Three of the nine patients with streptomycin resistant organisms at 120 days yielded sensitive tubercle bacilli about 2 months after cessation of treatment (loss of bacterial resistance) Bacterial resistance to PAS did not occur

Comparison with earlier studies showed that from the standpoint of delaying bacterial resistance streptomycin every third day with PAS daily is the preferred regimen However streptomycin every third day with PAS also every third day is superior to either drug alone for 120 days and is advantageous for patients unable to take PAS daily for long periods

Drug toxicity was not a major problem in either regimen Significantly less gastrointestinal disturbance was encountered with PAS administered every third day

[The possibility of improving specific antimicrobial therapy by using various combinations of drugs has been demonstrated Many combinations remain to be explored —Ed]

Value of Follow up Studies of Children with Primary Tuberculosis Edith M Lincoln[7] (New York Univ) reports 622 consecutive cases of primary pulmonary tuberculosis (1930-40) and follow up of survivors As a direct result of the first infection 149 (23 9%) died Meningitis caused 60% of deaths with less than 10% additional mortality from miliary tuberculosis without meningitis One fourth of the deaths were due to protracted hematogenous tuberculosis and locally progressive primary tuberculosis in approximately equal proportions These four complications of primary tuberculosis thus accounted for 95% of the mortality When streptomycin first became available the decision was therefore made to use it in primary tuberculosis only when one of the four major complications was present In the two years before streptomycin case fatality rate from primary

(7) Am R T be 64 499 507 N mbe 1951

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(6) D s Ch t 21 1 16 January 195

poor general condition Pronounced hyperventilation during rest exercise and recovery was always present Interference with oxygen transfer from alveolus to arterial blood arising principally from reduction in oxygen diffusing capacity of the lung was the most important and characteristic finding in this stage These physiopathologic characteristics were identical to those described in the syndrome of alveolar capillary block probably because of inflammation of the septal area as well as obliteration of some of the capillary bed Despite reduced oxygen diffusing capacity if alveolar ventilation is normal the pulmonary capillary blood may be almost fully saturated when the patient breathes ambient air at sea level because of the shape of the oxyhemoglobin dissociation curve in its upper portion Reduced lung volume must be caused by encroachment of the interstitial and intra alveolar exudate on the breathing space Conspicuous hyperventilation was noted in the absence of significant arterial anoxia and in the presence of normal or reduced arterial carbon dioxide tension The inflammatory pulmonary process could cause ventilatory stimulation via the pulmonary stretch reflexes and initiate hyperventilation resulting in lowering of arterial carbon dioxide tension and the alkaline reserve which increases sensitivity of the respiratory center for carbon dioxide Finally *the elevated physiologic* dead space *probably* was caused by persistent ventilation of areas where the inflammatory process had interfered with perfusion

Early in treatment this strong interference with oxygen diffusion improved and milder physiologic defects remained Interference with oxygen diffusion sometimes disappeared as early as three weeks after start of streptomycin therapy This correlates well with the observation that the earliest change in streptomycin treated tuberculosis is resorption of the acute exudate Reduction in all lung volumes persisted In only one case was there evidence of pulmonary emphysema Maximal breathing capacity was normal or only slightly reduced Hyperventilation during rest exercise and recovery if present was always mild Reduction of oxygen diffusing capacity was sometimes observed alveolar arterial gradients however were always smaller than those observed in the early acute phase The physiologic dead space was elevated Pulmonary arterial hypertension during mild exercise was

tuberculosis was 18% During the past four years case fatality rate was less than 3% although less than 25% of the ward population received streptomycin

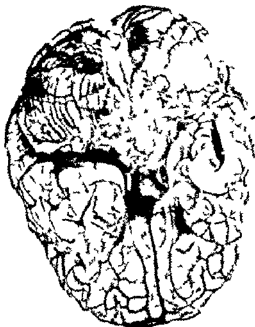
Factors influencing mortality were (1) age of patient (2) age of lesion and (3) extent of lesion Mortality exceeded 50% when tuberculosis was diagnosed in infants under 6 months, 28% at 1 2 years and 14% at 5 9 Approximately 90% of deaths occurred within 12 months of the first diagnosis of primary tuberculosis 75% within 6 months and almost 60% within 3 months Mortality with the largest lesions was more than double that with small primary foci

These 622 children and 378 others with x ray evidence of pulmonary tuberculosis that had begun to calcify were followed until age 25 to evaluate the nature of tuberculous reinfections Chronic pulmonary tuberculosis developed in 8% of survivors at intervals of 1 14 years after the first infection Over half the cases were in adolescents more than twice as many in females as in males In most girls the first roentgen abnormality was found within two years of menarche A child with recent primary tuberculosis should be followed closely in order to detect complications during the first year after infection Even during the so called safe period from one year after infection to adolescence however it is desirable to make roentgen studies at intervals because of the individual variation in time of development of late complications

[The pattern of tuberculosis in relation to age becomes increasingly apparent and the attack rate in adolescence is conspicuous It is unwise therefore to consider that all primary lesions become healed without harm. The meaning in relation to treatment is brought out by this report —Ed]

Cardiopulmonary Function in Hematogenous Pulmonary Tuberculosis in Patients Receiving Streptomycin Therapy was studied by John H McClement Attilio D Renzetti Jr Douglas Carroll Aaron Himmelstein and Andre Cournand[8] (Columbia Univ) in 11 cases at various intervals before during and up to three years after start of streptomycin therapy In the early exudative phase all lung volumes were reduced and there was no evidence of pulmonary emphysema Maximal breathing capacity was normal or somewhat reduced In some cases this reduction may have been related to

(8) Am. R T be c 64 583 601 De mbe 1951



F g 31 —B f pat t w th t be cul m g t wh d t pt my n f n m th T be cul p oc t t d l m d h w bu d f ect t as z d (C t y f A b h O Am Re T be 64 419 4 9 O t be 1951)



F g 3 —T b culou m g t ft 25 m th f t pi my th py M d ll bl ng t ou d d by d l y f by l d t ta g ea f t on (C t y f A b h O Am R T be 64 419 4 9 O tobe 1951)

observed in one case One or more of these functional ab normalities were present in all patients, even as late as three years after start of treatment These chronic derangements were identical with those described in the pulmonary fibroses associated with mild ventilatory insufficiency The innumer able small interstitial scars which remain in the healed stage cause reduction in lung volume mild hyperventilation and minor defects in ventilation perfusion relations characteristic of this type of pulmonary insufficiency

[This is one of the first studies of its type to reveal permanent altera tions which may be left after healing of tuberculosis under treatment The anatomic residues have been better known than the aftermath of physio logic disturbance —Ed]

Tuberculous Meningitis Correlation of Therapeutic Re sults with Pathogenesis and Pathologic Changes—*General considerations and pathogenesis*—Oscar Auerbach[9] (V A Hosp Staten Island N Y) reports that of 97 children under age 12 who died of some form of tuberculosis 42 2% had tuberculous meningitis It was usually related to spread from a primary complex Of 2 236 adults who died of tuberculosis tuberculous meningitis accounted for the deaths of 2 9% The disease was generally associated with acute generalized mili ary tuberculosis The difference between the pathogenesis of tuberculous meningitis in children and adults may explain in part the better results obtained in the former with strepto mycin therapy In children the source of dissemination is eliminated by healing of the primary infection whereas in adults meningitis is generally secondary to active extrapul monary tuberculosis which gives rise to repeated hematoge nous disseminations

Pathologic changes in untreated and treated cases—Auer bach[1] studied 64 cases of tuberculous meningitis in which streptomycin was administered both intramuscularly and in trathecally from 1 day to 25 months Dosages used were not available The survival period if no treatment is given is generally less than three weeks too early for extensive case ation and granulation tissue to develop With streptomycin therapy a new phase was introduced the exudate within the subarachnoid space underwent extensive necrosis which en circled and partially involved the vessel walls in a similar

(9) Am R v T berc 64 408 418 O tobe 1951
(1) Ib d pp 419 429

mycin has been made combined intramuscular and intrathecal routes must be used

At first alternate patients received streptomycin intra muscularly only and the others had combined intrathecal and intramuscular administration Later all patients were treated by the combined methods and treatment was gradu ally prolonged The following scheme finally was established Streptomycin (20 mg /lb body weight daily up to 2 Gm) is given intramuscularly for six *months* or until cerebrospinal fluid is normal It is given intrathecally (100 mg daily and

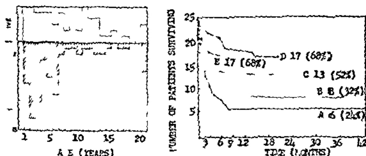


Fig 33 (left) —Ag d t h c (140 p t t
Fig 34 (ght) —S l t n g oup (A E) f 25 p t ents
(Court y f Calpa W L B t J T be 95 153 164 Octobe 1951)

more recently 50 *mg*) until the patient is clinically well (ex cept for irreversible lesions) temperature is below 99 F six weeks has elapsed since tubercle bacilli were last detected in the cerebrospinal fluid and the fluid is satisfactory (cell count below 100/cu mm protein below 200 mg /100 ml and falling and glucose over 40 *mg* /100 ml) Intrathecal treat ment is resumed if clinical symptoms or signs of activity reap pear cerebrospinal fluid level falls below 30 *mg* /100 ml on two successive occasions and tubercle bacilli are again isolated One patient may require six weeks of intrathecal treatment whereas another may require six months Twenty four patients have received sulphetrone intrathecally in addition to strepto mycin without improvement in survival rate Tapping the lateral ventricles has been practiced with increasing frequency and it is essential to have facilities available for making burr holes in the skull It *may* be a lifesaving procedure in an

process Concomitantly there was fibrous thickening of the intima of the enclosed blood vessels Tuberculous granulation tissue which developed from the pia arachnoid replaced the remaining fibrinocellular exudate in the subarachnoid space so that when prolonged therapy was given the base of the brain was covered by a dense layer of hyalinized connective tissue which enclosed necrotic foci (Figs 31 and 32) The course was similar to that in cases of tuberculosis of other serosal surfaces in which patients survived for long periods

[The frequency of relapse after initial control of tuberculous meningitis has been disturbing A number of reports emphasize this and also the fact that lasting recovery depends largely on early diagnosis and treatment The earliest diagnoses are made in cases of generalized miliary tuberculosis in which routine lumbar punctures may reveal abnormalities before the appearance of clinical symptom —Ed.]

Tuberculous Meningitis Some Experiences Based on Treatment of 140 Cases are reviewed by W L Calnan (London) Tuberculous meningitis may be present without physical signs of meningitis and sometimes even without symptoms The condition must be constantly kept in mind in all cases with miliary tuberculosis In such cases lumbar puncture is essential before and at regular intervals during treatment with streptomycin Puncture should be made at least once a month and preferably every week particularly during the first three months Symptoms of meningitis may not appear during intramuscular streptomycin therapy A tuberculin test should be carried out on all children with early vague symptoms If these persist for over a week chest x rays and lumbar puncture should be done Fever and mental apathy are important initial signs as well as the more classic signs of meningeal irritation such as headache vomiting fits squints neck stiffness and a positive Kernig sign However onset may be dramatic with convulsions

It is unnecessary and even inadvisable to delay beginning treatment until tubercle bacilli have been isolated from the cerebrospinal fluid The association of lymphocytosis with a low sugar content in the fluid occurs in no other condition except occasionally in neurovascular syphilis epidural abscess and torulosis It is unwise to start intramuscular treatment alone while waiting for tubercle bacilli to be isolated from the cerebrospinal fluid Once the decision to give strepto

(2) Brit J Tuberc 45 153 164 October 1951

cream of similar strength was applied superficially and re newed daily until the granulation tissue of the ulcer floor was clean This wa followed by application of a cream made up of 100 000 units calciferol/Gm Secondary infection an occa sional complication only rarely did not respond to local appli cation of a sulfonamide when there was an ulcer or a sinus or a single instillation of 10 per cent promanide jelly when the abscess wall was intact

The most notable effect was integrity of the skin Twenty seven patients showed no breakdown of the skin at any time during treatment Where a needle track sinus formed there was a tendency to spontaneous closure In over half the cases the pus was converted into serous fluid after the third or fourth instillation there followed steady diminution in size of the abscess with recovery of the physiologic texture and tone of the skin The familiar pathologic changes culminating in extrusion of the infected disintegrating lymph node were not seen The gland did not break down but could be pal pated as a firm nodule in the deeper tissues after resolution of the abscess If there was a sinus the discharge soon be came serous and the sinus closed fairly rapidly with minimal puckering If an ulcer was present there was a tendency to excessive formation of granulation tissue which however could be controlled by application of a cream containing 100 000 units of vitamin D concentrate/Gm NaPAS therapy also significantly decreased healing time as compared with other treatment methods (curettage or aspiration and ultra violet irradiation)

[Streptomycin is prefer d by many cl n cia for treatment of tuber culous aden ti especially following operation Necrotic nodes are not greatly influenced by an ant biot c but after the di ease has become well localized the nod may be removed and the drug will h lp to accelerate h al g and pre ent format n of postoperative sinuses —Ed]

PARASITIC DISEASE

Pulmonary Manifestations of Schistosomiasis is discussed by Abdel Aziz Sami[4] (Cairo Egypt) It is difficult to estimate the true incidence of endemic pulmonary disease Bilharzial cor pulmonale a manifestation of advanced pulmonary dis

(4) D Ch t 19 698 705 J 1951

attack of acute hydrocephalus and it provides an alternative route for administration of streptomycin in the presence of spinal block

Age distribution among the 140 patients is shown in Figure 33 Results of treatment in 114 are given in the table Only those with a minimum of 12 months observation are considered Figure 34 shows survival rates in successive

RESULTS OF TREATMENT IN 114 PATIENTS*

Group	Total	Deaths % of 114 Patients	Mortality (%) in Each Group
Under 3 yr	34 (30%)	25 (22%)	73
Over 3 yr	80 (70%)	36 (31%)	45
Early	36 (31%)	12 (10%)	33
Middle	50 (44%)	24 (21%)	48
Advanced	28 (25%)	25 (22%)	89

*Classification of [illegible] into [illegible] middle and advanced followed [illegible] scheme recommended by Medical Research Council 1948

groups of 25 patients Streptomycin resistant strains of tubercle bacilli were rarely isolated even on relapse The following sequelae were encountered deafness 15 patients retarded development (all under age 3) 6 hemiplegia 2 with minimal disability in 1 hemiplegia and homonymous hemianopsia 2 blindness 1 mental defect 2 Although deafness may be caused by the meningitis itself it has been more frequent since prolongation of streptomycin treatment Most of the deaf children would not have survived if the treatment period had been appreciably shortened Deafness must probably be regarded as the price these children have to pay for survival

Treatment of Tuberculous Cervical Adenitis with Para Aminosalicylic Acid G J Morris and R G Prosser Evans[3] treated 51 patients by aspiration and instillation of sodium para aminosalicylate (NaPAS) The abscess was aspirated by insertion of a large bore needle directly into its superficial wall Contents were completely evacuated and up to 1 ml of 20 per cent NaPAS was instilled into the cavity through the needle Aspiration and instillation were repeated weekly until the contents became serous and no additional pus formed If a sinus had formed along the needle track up to 1 ml fairly thick sterile jelly containing 20 per cent NaPAS was injected through the orifice of the sinus If a sinus ulcer developed a

(3) [illegible] 1199 1205 [illegible] 19[illegible]

simulate tuberculosis silicosis sarcoidosis atypical pneumonia or periarteritis nodosa Advanced cases with marked involvement of the heart and pulmonary artery must be distinguished from congenital atrial septal defect Pulmonary bilharziasis may be arrested at any stage and the patient may live his normal span of life For active bilharzial infection antimony (tartar emetic fuadin®) should be given but in advanced cases it must be given with caution Focal reactions in the lung are very frequent during antimony treatment and may be observed radiologically as a transient increase in the existing shadows Heart failure if present should be treated

Effects of Cortisone in Sarcoidosis Study of 13 Patients given cortisone for 28-106 days is reported by Louis E Siltzbach[5] (New York City) Daily dose was 100-150 mg five patients receiving the drug intramuscularly and eight orally All 13 patients improved subjectively or objectively but in none did the result approach a cure Response to cortisone was irregular and often transitory In the same patient some sites regressed while others remained refractory Of seven patients with severe disability five had significant relief from major symptoms in two regressive phenomena were limited to minor lesions In no patient was progression of lesions detected during treatment but 4 15 weeks is a short span in so chronic a disease In general fresh lesions seemed to be more amenable to therapy than older ones

Of 10 patients observed for 1 11 months after therapy 7 relapsed In three signs and symptoms were as severe as those present before therapy but the other four had only mild setbacks Relapse occurred as early as two weeks and as late as three months after treatment Of the three who did not relapse two had regression at all sites under therapy and had maintained the gains for 4 weeks and 4½ months respectively In the third only minor sites of involvement had responded to treatment and although these benefits endured the major disability was uninfluenced

All peripheral lymph node lesions receded during treatment and relapse was infrequent after cessation of therapy Mediastinal node involvement of relatively recent onset was apparently benefited but older nodal enlargements were not

(5) Am. J M d 12 139 160 F b ry 195

ease was recorded in 0.8% of 520 visceral bilharziasis cases and in 2.1% of 282 consecutive autopsies following schistosomiasis. Bilharzial lesions in the lungs were found by some authors in 33% of autopsies in cases of bilharzial infection. The disease is most prevalent in young adults between 20 and 35 but has been seen as early as age 12.

The bilharzia parasite can affect the lungs variously (1) Symptoms and signs of pulmonary irritation long described as "verminous pneumonia" may appear during the passage of the invading cercaria through the pulmonary circulation. (2) Allergic reactions characteristic of Loffler's syndrome may appear throughout infestation but particularly during the earliest stages, and especially among Europeans. (3) Asthma may also appear. In Egyptian patients, allergic reactions were rare. Instead the most striking and most frequent manifestation was embolism of the ova and occasionally of the worms themselves in the pulmonary circulation.

Nonallergic parenchymatous manifestations have hitherto been ill defined. Chronic bronchitis, emphysema, bronchiectasis and pulmonary fibrosis have been reported. Most important are the vascular manifestations. They constitute a clear cut picture of pulmonary vascular hypertension and eventually result in cor pulmonale. Bilharzial hepatosplenomegaly is usually present. The main complaint is general weakness. Some pallor from anemia may appear but cyanosis does not. This striking difference from Ayerza's disease, which it otherwise resembles, is explained by the localization of lesions in the pulmonary arterioles leaving the capillaries and alveoli free.

Three grades of roentgen changes have been described. (1) intensification of shadows of one or more of the second or third degree arteries, mostly the basal ones. (2) clusters of mottling in relation to the arteries giving the lung fields a granular background and beginning changes of cardiac outline and (3) more severe lesions and patches of localized opacity. In this last stage the pulmonary conus and trunk balloon and may reach aneurysmal size. The heart configuration is typical of cor pulmonale.

Diagnosis rests on the clinical and x ray pictures and evidence of bilharzial infection. The pulmonary shadows may

was seen in pretreatment sections no ascertainable increase was found after therapy

[Some evidence suggests that corti one might accelerate fibrosi of pulmonary sarcoid lesions perhaps increasing permanent dy function from this cause Corti one therapy mu t still be considered to be in the stage of investigation —Ed]

BRONCHIECTASIS

Prebronchiectasis H B Harwood[6] (Sydney) notes that 65% of all cases of bronchiectasis develop in the first two decades of life i e when the patient usually has the infections which so often precede its onset Hence it is among young children that most preventive work must be carried out A prebronchiectatic patient is one who has had a respiratory infection and has been left with a cough not always produc tive for 8 10 weeks after the infection—particularly when added to this nasal discharge is present and he is allergic or has a family history of allergy Some of these patients give a much longer history of cough but may still be prebronchiec tatic In a young child a productive cough may not produce any obvious sputum Although sputum is usually expectorated after age 8 the younger child more often swallows it and under age 3 this is almost always the case There may also be low grade fever and physical signs may be present at the lung bases The masking effects of antibiotic agents should not be overlooked All these patients should have an x ray examination of the chest and nasal sinuses but even if it is negative the patient s history makes vigorous treatment es sential

The best treatment is preventive First predisposing in fections should be thoroughly treated Careful observation during convalescence postural drainage preceded by inhala tions and avoidance of opiates will prevent progression of prebronchiectasis Early complete drainage of the bronchi is essential It has been shown that in cases in which inflamma tory stenosis was short bronchograms were normal after one or two bronchoscopic aspirations

Of 50 patients with prebronchiectasis 30 had a suggestive history but normal bronchograms and 20 showed slight dila

(6) M J A t al 2 258 264 A g 25 1951

There was clearing of fresh pulmonary lesions but not of older ones. Symptomatic and roentgenographic relapse occurred in a fair proportion after the drug was stopped. Ocular lesions responded dramatically when the uveitis had not progressed to irreversible scarring. There was no change in size of liver and spleen. In one patient a skin lesion present for four years began to spread four weeks before therapy was started. Though it did not entirely clear, seven weeks after



Fig. 35 (left).—Section of lymph node removed before therapy shows large bland epithelioid cells giving mosaic pattern, crowding the lymphoid tissue. × 155.
Fig. 36 (right).—Same case. Section of lymph node removed after therapy shows dense cellular whorls of hyalinized connective tissue. × 155.
(Courtesy of Schaumbach, E.: Am. J. Med. 12:139-160, February 1952.)

therapy it remained pale and flat. In one patient with huge parotid glands for a month the glands began to recede after one week's therapy and were no longer palpable after eight weeks. There was also regression of subcutaneous nodules in two patients (one of whom relapsed after therapy) and in one lesion which caused narrowing of the bronchus. The effect on a spinal cord lesion was transitory. Post-treatment biopsies showed hyalinization in all specimens but two (Figs. 35 and 36). In the one patient in whom extensive hyalinization

Allergic sensitivity of the bronchi could be increased or decreased by varying the amount of inhalant Hyposensitization was achieved with minute amounts of allergen causing a mild but distinct asthmatic reaction and by gradually increasing these amounts sometimes in the course of as many as 17 experiments Two patients with pure grass pollen asthma two affected by other pollen six allergic to house dust and three with mold asthma were all hyposensitized by this method Eleven other patients showed uncertain results seven others could not be hyposensitized Two patients allergic to grass pollen had recurrence of eye and nose symptoms of hay fever but no asthma

An unusually large antigen dose not only caused a strong asthmatic attack but also hypersensitivity The hypersensitive state may persist unchanged for a long time if no more antigen reache the patient but much more severe reactions are likely when more antigen reaches him This was shown in one patient When much smaller quantities of antigen are inhaled the patient s hypersensitivity may be gradually changed to hyposensitization Spontaneous changes in the severity of allergic asthma may result from repeated interchange of natural hyper and hyposensitization Suppression of allergen induced asthmatic attacks with isoprenaline neither interfered with the progress of hyposensitization nor prevented hypersensitization

Asthmatic attack could not be induced by bacterial vaccine

Bronchial Asthma in the Farm Population Leon Unger[9] (Northwestern Univ) studied 53 patients who were farmers or lived on or close to farms 45 with bronchial asthma 23 perennial allergic rhinitis or perennial hay fever and 19 hay fever 27 had more than one condition Intradermal or scratch tests were done with various dusts The latter are more reliable and less likely to give false positive results More than half the patients had positive reactions to the dust of hay straw barns grain mills hen houses corncribs and oatbins Further tests were made with other substances common to farms and with certain nonfarm allergens Forty nine patients had positive reactions to ragweed pollen with symptoms during August and September Ragweed grows on farms in the middle of the crops and to protect themselves farmers must

(9) P tg d M d 10 42 48 J ly 1951

tation and crowding of bronchi in bronchograms In addition to the usual therapy, bronchoscopic aspiration and lavage were done in all patients The 30 patients received an average of 5 bronchoscopic treatments and the 20 patients an average of 13 It appeared that this procedure prevented irreversible bronchiectasis

[*There is still considerable disagreement about the initial cause of the change in the bronchial wall leading to bronchiectasis but it is generally recognized that after the change has occurred the hazard of repeated infection grows Once the diagnosis has been made therefore it is important to anticipate this possibility and direct efforts toward prevention and early treatment. Resection of course is the only cure of the fundamental defect —Ed*]

BRONCHIAL ASTHMA

Bronchial Obstruction Induced by Allergens, Histamine and Acetyl beta methylcholine Chloride Attacks were induced by Herbert Herxheimer[7] (Univ College Hosp London) in asthmatics by the inhalation of aerosols of histamine, acetyl beta methylcholine chloride pollen and mold extracts and house dust antigen their severity was measured by estimation of the vital capacity Those induced by histamine and acetyl beta methylcholine chloride developed suddenly and violently Sensitivity to both substances was much greater than in normal subjects and showed marked individual variation Attacks induced by pollen and dust antigen developed gradually sometimes many hours after inhalation and became increasingly severe Attacks induced by molds usually showed no latency or late effects and subsided spontaneously

Bronchial Hypersensitization and Hyposensitization in Man Inhalation of allergenic extracts from a closed spirometer circuit was used by Herbert Herxheimer[8] (Univ College Hosp London) for testing directly the allergic sensitivity of the bronchi in 32 asthmatic patients Allergens were selected according to individual history A patient with typical hay fever starting early in June and lasting four weeks was tested with mixed pollen whereas one who suffered most in winter was tested with house dust and molds Intervals between successive experiments were usually 7 or 14 days but sometimes longer

(7) Internat A h All gy 27 39 1951
(8) Ibid. pp 4? 59

asthma) and mortality is 8 10% (1% in the allergic type) Difficulty in distinguishing the two types is due mainly to three factors (1) After allergic asthma in the early decades and a free interval of many years asthma may return The patient may have lost his hypersensitiveness to the usual allergens there may be a change from the allergic to the non allergic type but the reverse is almost never true (2) Positive skin reactions may have no significance unless confirmed by exposure to or elimination of the allergen (3) Concomitant vasomotor rhinitis is not necessarily diagnostic of allergic asthma but may accompany nonallergic asthma when its onset is in the later decades

The cause of nonallergic asthma is unknown That it is due to allergy to bacterial products is unproved The main treatment aims at removing the thick mucus the principal lesion Potassium iodide 2 3 Gm daily for the first few days greatly lessens its viscosity Release of bronchospasm by epinephrine ephedrine and aminophylline given intravenously or rectally permits the thinned out mucus to be coughed up Mucosal edema is the least important factor for which an antihistamine may be used Secondary bronchial infection common in many of these patients should be treated adequately when symptomatic treatment is instituted because pus obstructs the bronchioles still more Once the airways are freed from obstruction asthma ceases In many cases the underlying factors continue to operate but potassium iodide and ephedrine compounds taken once or twice a day usually keep the patient comfortable Many patients after having been relieved once may require no medication but recurrence is not unusual By such symptomatic therapy many patients can be freed of severe asthma and may remain so Not only does such treatment give relief but it prevents serious complications

Pulmonary Function in a Group of Young Patients with Bronchial Asthma Daniel S Lukas (New York Hosp) studied six patients aged 11 16 at times when they felt free from asthmatic symptoms All had had perennial attacks of asthma and all had one or more allergies Mild attacks of bronchial asthma had usually preceded the study by a few days to several weeks

(2) J All gy 411 4 S pt mb 1951

pull up the weeds cut or destroy them before August 10-15 Forty four patients were sensitive to molds found outdoors especially alternaria and hormodendrum and 42 were sensitive to smuts Twenty were sensitive to chenopod pollens 19 to grass pollen 12 to home pets and 10 to tree pollen Although most patients came from farms where corn was the main product only four were allergic to corn pollen the largest of all pollens Thirty three were sensitive to farm animals 25 to horses 12 to cattle and only 4 to hogs In addition some *were sensitive to feathers*

Specific treatment gives best results in bronchial asthma *In these cases* it included elimination of the allergen as well as injections of the particular extracts to which the patients were sensitive and which fitted in with their clinical symptoms Results were excellent in 28% good in 47% fair in 19% and poor in 6% Even when results were excellent complete freedom from symptoms could not be achieved as long as the patients remained in contact with allergens

Nonallergic Bronchial Asthma According to Harry L Alexander[1] (Washington Univ) the distinction between allergic and nonallergic asthma is of far greater importance than mere academic interest as in the latter no amount of environmental or dietary control is of real benefit Distinction is not always simple for the two types closely resemble each other *Perhaps the first step is to be assured that the patient* has true bronchial asthma Diagnosis is made by examining *the sputum A specimen coughed up consists of tough* sticky mucus which if shaken up vigorously in saline solution fragments *into many small strands and spirals* when *one of these* is spread on a glass slide and stained with eosin and methylene *blue* myriads *of eosinophils appear Except for tropical* eosinophilia and Loffler s syndrome—both very rare—nothing else gives this picture With complicating bronchial *infection* these are eosinophils pus cells and bacteria In chronic bronchitis there are few if any eosinophils instead *mostly pus* and bacteria are present

In nonallergic asthma there is usually no family or past history of allergy significant skin reactions or response to an antiallergic regimen Onset is usually in the middle or later decades intractable asthma is common (but rare in allergic

(1) Postg d M d 10 117 121 August 1951

M B C was found reliable Performed before and after bronchodilation it was most sensitive to any obstruction in the smaller bronchial passages If the obstruction is kept at a minimum by adequate therapy the high incidence of emphysema among bronchial asthma patients may be reduced

Delirium and Coma Precipitated by Oxygen in Bronchial Asthma Complicated by Respiratory Acidosis In some patients an increase in the arterial carbon dioxide content occurs during and after breathing 50 100 per cent oxygen This is most marked in patients with structural pulmonary emphysema or fibrosis of the lung in which chronic hypoxemia hypercapnia and acidosis exist Indeed such patients may become delirious stuporous or comatose when oxygen is administered in high concentrations Henry D Beale Irving W Schiller Meyer H Halperin William Franklin and Francis C Lowell[3] (Boston Univ) report on a case in which such coma occurred although asthma was the only pulmonary disease present and pulmonary functions were normal after asthma was relieved

Man 53 was admitted in October 1949 because of repeated asthmatic attacks which first appeared in February 1949 and the last of which had not been completely relieved Laboratory studies were not remarkable venous carbon dioxide content was 34 and chloride concentration 93 5 m Eq /L Chest x ray films taken on admission showed numerous cattered calcifications at the hili and in the parenchyma of both lungs with no evidence of active tuberculosis There were moderate bronchial thickening and peribronchial infiltration at the right base Films taken in January 1950 showed no change in the appearance of the lungs but those obtained in maximal inspiratory and maximal expiratory positions showed good motion of the diaphragm and chest wall and seemingly adequate ventilation

He re ponded poorly to the usual asthma treatment Beginning November 7 continuous oxygen by nasal catheter was given for several days and he became drowsy confused finally refused to take oxygen and seemed better without it He continued to receive vigorou treatment with drugs and was given large doses of cortin Cortin was of questionable value but he improved somewhat Since the deleteriou effect of oxygen was not yet suspected he was given oxygen intermittently for respiratory distress and with similar results On November 30 when he again had severe asthma he was g ven continuous oxygen by nasal catheter 6 L /*minute Over* a per od of eight hours he became progressively less responsive and finally comatose The role of oxygen was suspected and when oxy

(3) N w E gl d J M d 244 710 714 M y 10 1951

Vital capacity significantly diminished in three patients Average residual air volume increased considerably the ratio of residual air to total capacity averaged 41 8 per cent and exceeded 35 per cent in four patients Average total capacity increased only slightly and greatly overexpanded in only one patient A bronchodilator increased vital capacity in only two subjects In one a striking 1 013 cc increase occurring after epinephrine was given presumably diminished the increased residual air volume by a similar amount thereby completely reversing the emphysematous state of the lungs Ventilatory capacity as measured by maximum breathing capacity (M B C) showed a greater reduction from normal than did vital capacity Significant increases of M B C were observed in all patients except one following epinephrine or vaponefrin in only one patient did it attain normal There was an average 29 1 per cent increase in M B C as compared to a 5 9 per cent increase in vital capacity following bronchodilation

Hyperventilation was present in all patients at rest and was particularly marked during exercise Since oxygen consumption during both rest and exercise was normal hyperventilation was associated with an inefficient oxygen removal rate per liter of air ventilated Underlying this inefficient gas exchange was a definite disturbance of air distribution throughout the lungs Thus the index of intrapulmonary mixing was on the average slightly elevated and in half of the patients definitely above normal More significant physiologic evidence of disturbance in air distribution among the alveoli was arterial anoxemia in three of the five patients whose arterial blood was examined The normal blood carbon dioxide contents did not suggest chronic respiratory acidosis Indeed carbon dioxide content during rest tended to be low and was compatible with hyperventilation

These observations indicated that bronchiolar obstruction and presumably increased intra alveolar pressures persist in recurrent asthma patients after acute asthmatic episodes have subsided The severity of persistent obstruction in the bronchial tree and the duration and frequency of acute asthmatic attacks may determine the development of emphysema Pulmonary function tests as a guide to the management of such patients are highly desirable Among easily performed tests

general translucency of the lung fields on posteroanterior films Marked overtranslucency indicates an asthmatic origin

The heart is usually small in posteroanterior films and the cardiothoracic ratio is reduced A gap is frequently visible between the diaphragm and the left ventricle These changes are believed to be entirely due to the low diaphragm and are most marked in asthmatic subjects in whom they can be regarded as some guide to the severity of the emphysematous change In two thirds of the patients examined the pulmonary conus was enlarged and in one fifth the right ventricle but the presence of radiologic cor pulmonale has no bearing on severity or etiology If pulmonary heart failure supervenes the cardiac silhouette becomes generally enlarged

Though emphysema can be readily detected radiologically and though radiography may be invaluable in ascertaining the cause of the emphysematous change the degree of emphysema can be much more accurately assessed clinically and spirometrically than radiologically

[Many studie have been conducted on the mechanisms of emphysema which is one of the important di abling condition of late life It may be assumed that better understanding will help to provide means of preventing the more serious phases and of relieving much of the discomfort Some patients may be taught to adapt th mselves to the limitations of emphysema and also by voluntary control to use their breathing apparatus w th improved effect on ventilation —Ed]

Use of Artificial Respiration in Pulmonary Emphysema Accompanied by High Carbon Dioxide Levels H J Boutourline Young and J L Whittenberger[5] (Harvard Univ) describe the use of the body respirator in two patients with severe emphysema accompanied by high carbon dioxide levels Although results were disappointing in one patient the effects on the other were so dramatic that recommendation for further trial of the therapeutic procedure seemed warranted

CASE 1 —Man 58 was hospitalized in 1950 with persistent headache somnolence dyspnea on exertion and ankle edema When first admitted in 1947 with similar complaints he had marked emphysema with secondary polycythemia arterial oxygen saturation of 82% mild cor pulmonale and serum carbon dioxide content of 49 mM /L In 1950 he was cyanosed orthopneic and confused Respiration was shallow with a prolonged expiratory phase The chest had an emphysematous appearance with increased anteroposterior diameters and was hyper resonant throughout Roentgenograms showed smooth low diaphragms which moved equally Lung

(5) J Cl I t 30 838 847 A g t 1951

gen was discontinued the patient awakened although he became cyanotic

Studies made then and subsequently showed hypoxemia hypercapnia and acidosis When oxygen was administered the hypoxemia was relieved but carbon dioxide retention was increased and acidosis became more severe Following several courses of cortisone the patient finally improved and became free of symptoms Pulmonary function studies performed then were normal

[The misuse of oxygen in critical situations is becoming more widely recognized The reason for possible ill effects is better understood enabling the physician to anticipate and avoid trouble —Ed]

EMPHYSEMA

Correlation between Radiologic Appearances and Clinical and Spirometric State in Emphysema Fifty two emphysema patients eight of them asthmatic were assessed by A G W Whitfield O E Smith D G B Richards J A H Waterhouse and W Melville Arnott[4] (Univ of Birmingham) in an endeavor to correlate radiologic appearances and clinical state All patients showed some radiologic abnormalities the most constant being depression and flattening of the diaphragm These features were not accurately related to the severity of the disease and in the absence of bronchospasm restriction of the respiratory excursion of the diaphragm was the most valuable radiologic index of the degree of emphysema Hilar descent on inspiration is also a valuable radiologic sign Calcification of the costal cartilages was the same as in normal subjects Kyphosis was present in only one of the asthmatic group but is seen often in those whose emphysema has other causes The radiologic chest volume is increased as a result of both diaphragmatic depression and increase in anteroposterior diameter of the chest It is of little value as an index of severity The transverse diameter of the chest is not increased and the rib level of the diaphragm is the same as in normal subjects The low diaphragm is therefore a visual impression and does not lend itself to rapid quantitative assessment Overtranslucency of the lung fields is usually present in *emphysema but the relative brilliancy of the lung* bases and the translucency and area of the retrocardiac and anterocardiac windows are more important guides than the

(4) Q J Med 20 47 260 J ly 1951

the patient exhibited no diminution in breathing on receiving 90% oxygen but some 36 hours after leaving the respirator the earlier diminution in breathing again appeared

Some Effects of Adrenocorticotrophic Hormone and Cortisone on Pulmonary Function of Patients with Obstructive Emphysema Daniel S Lukas[6] (New York Hosp) made studies before and during administration of ACTH and cortisone in nine patients with various types of chronic lung disease Subjective and objective improvement sometimes dramatic occurred in patients whose disease was secondary to or complicated by bronchiolar obstruction This observation with the pattern of change in pulmonary function suggested that ACTH and cortisone exerted a sustained bronchodilating action They may decrease reactivity of the bronchiolar musculature to allergens and cause subsidence of chronic inflammatory changes in the bronchial mucosa much as ACTH and cortisone cause such changes in diseased nasal and sinus mucosa

These agents had greater effect than conventional bronchodilators on the bronchial tree in at least two patients with chronic obstructive emphysema they also helped to reveal the true extent to which functional impairment could be attributed to bronchiolar obstruction rather than to permanent anatomic changes Minimal responses to the hormones in patients with no bronchiolar obstruction strengthens the impression that ACTH and cortisone act in a general sense as bronchodilators There is little reason therefore to expect that these agents will affect degenerative or senile emphysema Further depression of gas exchange encountered in a patient with cor pulmonale was thought to reflect the development of edema of the alveolar membrane Such side effects are hazards of ACTH and cortisone administration in far advanced chronic lung disease

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PNEUMOCONIOSIS

Pulmonary Distribution of Radioactive Particles in Rabbits after Inhalation and Intravenous Injection Bacillus subtilis spores have an ideal size range (0 5 1 5 μ) for pulmonary penetration studies The greatest difficulty encountered in de

(6) Am R T b 64 279 294 S pt mbe 1951

markings were increased and costophrenic angles were clear Blood urea nitrogen was 17 39 mg /100 ml serum carbon dioxide 35 3 41 4 mM /L chlorides 83 91 m Eq and total base 139 m Eq /L When he was given oxygen cyanosis disappeared but ventilation was decreased so that arterial pCO rose from 67 to 76 mm Hg and his condition visibly deteriorated He was placed in respirator for four days On the second day when high oxygen was given breathing was still depressed as indicated by rise in pCO_2 from 46 to 52 mm Hg Subsequent values for ventilation were high and were accompanied by reasonably low alveolar pCO Analysis of arterial blood 5 days and 11½ months after respirator treatment with the patient breathing room air gave a slightly subnormal pCO and arterial oxygen saturations of 92% on both occasions Oxygen no longer elevated pCO_2 in fact ventilation may have been stimulated during oxygen administration by the patient s enthusiasm to demonstrate his ability After leaving the hospital he progressed satisfactorily returned to his job became free from headaches formerly a major symptom and could climb a flight of stairs with only slight dyspnea

Case 2—Man 52 was hospitalized with shortness of breath and wheezing He had had emphysema for six years and two years earlier unilateral hydronephrosis had been diagnosed Dyspnea on exertion had increased and recently he had been unable to take three level steps without gasping The dyspnea varied greatly from time to time A chronic cough with whitish sputum and intermittent wheezing had been present for years The patient was cyanotic and dyspneic Chest x ray showed low diaphragm and emphysematous lung fields Blood nonprotein nitrogen was 21 mg /100 ml chlorides 82 mEq and serum carbon dioxide 40 mM /L When oxygen was given alveolar pCO rose rapidly from an average of 53 to 75 mm Hg while ventilation fell When given a mixture of 94 75% oxygen and 5 25% carbon dioxide for five minutes his ventilation progressively reduced

Respirator therapy given for five days after a short preliminary treatment for eight hours gave no benefit Efforts to increase ventilation proved difficult even when a pressure change of 30 cm water was produced in the respirator and various other devices to encourage breathing were employed The patient apparently resisted all of these devices by skilful use of the glottis Nevertheless arterial and alveolar pCO_2 showed a downward trend Three determinations of alveolar and arterial pCO_2 averaged 41 and 40 mm Hg respectively Alveolar pO_2 at the same time was 106 mm Hg while arterial pO had risen to 55 mm Hg The arterial oxygen saturation on room air was 85% The patient did not maintain this relatively satisfactory condition after removal from the respirator On the two days following arterial pCO_2 rose to 50 and then to 64 mm Hg while the pO_2 descended to 28 mm Hg a saturation of only 48% on room air The arterial alveolar oxygen difference rose to 62 mm Hg On the first day out of the respirator

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(6) Am R T b 64 79 294 Sept mbe 1951

termining their pulmonary distribution is microscopic identification This led George V Taplin James S Grevior Mary Louise Gautschi Camille Finnegan and Arthur Dunn[7] (Univ of California) to tag the spores with P^{32} and detect distribution in the lungs by measuring beta activity Rabbits exposed to atmospheres in which suspensions of the spores had been aerosolized were killed at various intervals and depth of penetration of radioactivity *into the lung was estimated*

Tagged spores were cleared from the trachea in 1 2 hours but remained in the lung parenchyma for at least *72* hours Activity remaining in lung tissue at *72* hours probably represented spores that penetrated beyond the area where the respiratory lining membrane is ciliated Solutions which contained P^{32} and suspensions of tagged spores were injected intravenously When P^{32} was incorporated in the spores the isotope was localized in high concentration in lung liver and spleen whereas with the isotope solution beta activity was highest in kidneys and liver and relatively low in lung and spleen This characteristic difference in distribution pattern between solutions and particulate suspensions verified the effectiveness of the tagging procedure and also demonstrated that 1 μ particles are removed from circulation mainly by the liver P^{32} tagged B subtilis spores were deposited and retained in the trachea and lungs of rabbits in a distinctly different relation after inhalation from that after intravenous injection The inhalation pattern was characterized by relatively high tracheal values *compared with those in the lung* whereas the distribution pattern after intravenous injection showed low tracheal and high lung values Further after inhalation the trachea was cleared rapidly but after injection there were no significant tracheal changes in the first 24 *hours* The *pulmonary parenchyma is relatively slowly* cleared after both modes of administration although the mechanisms are not the same Ciliary activity probably plays the major role after inhalation and phagocytosis after intravenous injection A single short inhalation exposure to insoluble *radioactive particles about 1 μ in size may be hazardous* However the normal lung clearance mechanisms are highly efficient and act within one to two hours to remove foreign

(7) [illegible] All[illegible]gy 9 703 713 N[illegible] Dec 1951

material initially retained in the tracheobronchial tree of rabbits

Pleural Calcification Resulting from Exposure to Certain Dusts Adelaide Ross Smith[8] (New York State Dept of Labor) reports that a roentgen survey of occupational groups exposed to various dusts showed the highest incidence of pleural calcification in those exposed to dust involved in making Bakelite insulators (1 5% of 197 workers) calcimine (1 7% of 114) mica (1 6 % of 302) and tremolite talc (6 3% of 221) The first two groups were exposed to mixed dusts which included talc and mica so that talc and/or mica dust may have been responsible for calcifications in all four groups The type of calcific plaque varied from a single linear appearing deposit a few centimeters long in the region of the diaphragm to massive bizarrely shaped deposits extending over a large part of both lung fields Among the mica workers in addition to calcific pleural deposits a conspicuous proportion showed excessive calcification of the hilar lymph nodes

Clinical examination and questioning of tremolite talc workers with pneumoconiosis and those with calcific pleural plaques failed to show any definite correlations between the presence of calcific deposits and age length of exposure or history of previous respiratory disease Study of 14 talc workers with calcific deposits revealed the following facts Ages varied from 35 to 77 and period of exposure from 4 to 52 years Only one person gave a history of pleurisy None had had empyema or any serious chest injury In five persons no pulmonary involvement other than the calcific plaques was noted In seven there was an accompanying pneumoconiosis Evidence of clinically significant tuberculosis was seen in two patients and of primary healed tuberculosis in one other Symptoms and signs occurred only in persons who also had other lung involvement

Tremolite talc is a calcium magnesium silicate Physically its fibrous structure closely resembles asbestos The combination of calcium and magnesium distinguishes tremolite talc and muscovite mica from asbestos another pneumoconiosis producing dust which is likewise a magnesium silicate but does not cause pleural calcification Magnesium ions have a

(8) Am J Roe tg 1 67 375 38 M h 1952

greater activating effect on all animal phosphatases than any other cations Phosphatase in turn plays a part in making available phosphate ions necessary for deposition of calcium phosphate hence factors favoring an increase in phosphatase will favor calcium deposition It is possible that these substances produce calcific pleural deposits in relatively high proportion because in addition to being capable of causing pneumoconiosis with associated pleural irritation they also contain calcium and magnesium which tend to promote calcium deposition

[The explanation of these peculiar pleural calcifications is not clear In the general population the commonest cause is an old hemothorax or tuberculous empyema Extensive calcification usually associated with fibrous organization of the pleura *may interfere* considerably with the ventilatory motion of the thorax —Ed]

Epidemiology of Beryllium Intoxication is discussed by James H Sterner and Merril Eisenbud[9] (U S Atomic Energy Commission) Acute beryllium poisoning has been reported from exposure to beryllium metal beryllium oxide sulfate fluoride hydroxide and chloride Physical properties of beryllium oxide and its manner of preparation determine its ability to produce acute pneumonitis Oxides prepared by low temperature calcination are much more reactive than those prepared at higher temperatures Acute pneumonitis can result from single exposures to beryllium compounds and is associated with concentrations which exceed 100 μg/cu mm A reasonably clearcut relationship exists between the incidence of acute disease and severity of exposure

Chronic beryllium poisoning (berylliosis) has followed very minimal exposure Residents near a beryllium producing plant contracted berylliosis on exposure to concentrations as low as 0 1 μg/cu mm In the plant s vicinity a clearcut relationship existed between exposure and incidence of disease Incidence approximated 1% within ¼ mile and fell off rapidly with none attributable to air pollution beyond ¾ mile from the plant However of 1 700 individuals who at some time had been employed there only six (0 3%) were known to have had berylliosis despite the high incidence of acute disease in this group None of the six had been exposed for more than four months Berylliosis probably developed only among persons exposed also to beryllium oxide

(9) A M A A h I d t Hyg 4 123 151 A gust 1951

Contact dermatitis beryllium ulcer and acute involvements of the respiratory tract (rhinitis tracheitis bronchitis acute pneumonitis) after beryllium exposure conform to conventional patterns of occupational disease Beryllium is both a primary irritant and a skin sensitizer Acute respiratory reactions conform to the pattern produced by such respiratory irritants as phosgene or nitric oxide Berylliosis however departs markedly from these patterns (1) Severe illness has followed exposures far lower than is common with known industrial toxins (2) Autopsies have revealed a wide range of tissue concentrations and no relationship was evident between the amount of beryllium present and the extent of disability or pathologic involvement (3) At atmospheric concentrations under 1 μg/cu mm incidence varies directly with exposure but no such relationship is demonstrable for much higher concentrations (4) Symptoms frequently appear years after exposure (5) Pulmonary berylliosis lesions have not been produced experimentally Berylliosis is more readily understood as a modified immunologic reaction Beryllium combined with protein forms an antigen which in turn produces a beryllium specific antibody The subsequent reaction of beryllium and this specific antibody causes inflammation and exhibits a high degree of organ specificity With beryllium oxide retained in the lung a shock response once begun will continue with a severity dependent on the degree of tissue sensitization and on the rate of release of beryllium from the tissue deposit Since sensitization may sometimes occur only after prolonged contact the delay between final exposure to beryllium and onset of symptoms becomes clear and the disparity between lung content of beryllium and the severity of lesion becomes understandable Other tissues with small beryllium deposits can exhibit the antigen antibody reaction Thus granulomas in the liver skin and other organs become clear Significantly skin granulomas in berylliosis patients were not noted until pulmonary symptoms began to develop

Effect of Bituminous Coal Dust and Smoke on the Lungs —Animal Experiments I Effects on Susceptibility to Pneumonia was studied in rats by Frederick J Vintinner and Anna M Baetjer[1] (Johns Hopkins Univ) Inhalation of bituminous coal dust instead of increasing susceptibility to lobar pneu

(1) A M A A b I d t Hyg 4 06 16 S pt mb 1951

monia produced by intrabronchial injection of type I pneumococci suspended in mucin increased resistance The protective mechanism was lacking when the organisms were given intrabronchially *in broth* and led primarily to rapidly developing septicemia rather than to lobar consolidation These results coincided with previous findings testing the effect of silica (quartz) and feldspar dust In coal dust experiments the protective mechanism appeared after 14 or more days of exposure but in silica and feldspar experiments it was evident after only a few days as well as after exposure over longer periods

Since organisms injected in broth produced no protective effect the effect of dust exposure was related to mucin action on the organisms Few pneumococci are required to produce infection when injected in viscous mucin solution apparently because the mucin protects them from the body s defense mechanisms The dust may have absorbed the mucin or altered its physical or chemical properties so that the organisms were more susceptible to body defenses Perhaps dust particles stimulated mobilization of lung macrophages thus increasing local resistance against bacteria but this should also have been evident with broth injected organisms unless the dose was in this case overwhelming Inhalation of the smoke of bituminous coal did not appreciably affect the rats resistance to the pneumococci whether injected in broth or in mucin The protection was therefore probably associated only with the presence of coal dust in the lungs Autopsies showed that exposure of rats to coal dust and smoke for over 20 weeks somewhat increased the incidence of spontaneous lung disease but the weight of mature rats was unaffected

Effect of Tobacco on Lung Volume Total lung volume and its subdivisions were determined in 58 healthy men by A G W Whitfield W Melville Arnott and J A H Waterhouse[2] (Univ of Birmingham) and the results correlated with present and past use of tobacco Smoking produced a slight diminution in vital capacity and a more pronounced increase in residual air and in the ratio of residual air to total lung volume The effects were much more evident in sub

(2) Qu t J M d 0 141 147 Ap 1 1951

jects whose recent use of tobacco had been high *Smoking also* produced diminished chest expansion

[A familiar effect of excessive smoking is cough and expectoration which reflects some bronchorrhea and probable edema of the bronchial mucosa This may interfere particularly in susceptible individual with free passage of air —Ed]

NEOPLASMS AND ANOMALIES

Bronchogenic Cysts R J Healy[3] (MC AUS) reports 19 cases Physical examination of the chest usually gave negative results Pressure symptoms such as dyspnea cyanosis



F g 37 (l ft) —O l fl d filled th w ll d y t g f m ght m n t m h h man 32 w th t ympt m
F g 38 (ght) —I f t d y t ta g d fl d d t m t w h b h n m 30 w th t h ll d f d p d t gh
(C tesy f H ly R J R d l gy 57 00 03 A g 1951)

cough wheezing chest pain and dysphagia varied with size and location of the cyst If infection supervened chills fever cough — usually productive — and leukocytosis appeared About 50% of the patients were asymptomatic the lesion being found on a survey film Most of those presenting symptoms recalled previous episodes of illness diagnosed as bronchitis asthma pneumonitis lung abscess or other chest condition

Roentgenographically the cyst was demonstrable as an

(3) R d logy 57 200 03 A g t 1951

ovoid mediastinal or intrapulmonary mass of homogeneous density though occasionally fluid and air were distinguished The margin was smooth and discrete and the surrounding lung field usually normal Most of the cysts were single Location was along the trachea or larger bronchi from the sternal notch to the diaphragm In a few instances gradual increase in size was observed Of chief diagnostic significance were the ovoid shape and change of shape on inspiration and expiration films The shape was accounted for theoretically by the single point of attachment to the bronchial tree and the gravitational pull of the fluid contents (Figs 37 and 38) Fluoroscopy showed (1) movement of the cyst on swallowing if it was attached to the trachea (2) deviation of the barium filled esophagus when the cyst was in the posterior mediastinum (3) transmitted pulsation if the cyst lay adjacent to the heart or great vessels Bronchograms were of little diagnostic aid since they usually revealed only displacement of the bronchi by the mass An occasional cyst may fill partially with the opaque medium thereby demonstrating its cystic nature the plain film however showed that such cysts contained both fluid and air

Bronchial Adenoma Analysis of 26 Cases is reported by N C Delarue[4] (Univ of Toronto) Typically the lesion is seen in a patient usually under age 50 with long history including endobronchial symptoms prominent and emphasis on hemoptysis and recurring attacks of lower respiratory infection Obstructive atelectasis can be verified on x ray films The lesion visible on bronchoscopy occurs in a major bronchus significantly more often than carcinoma Since this adenoma syndrome has a prolonged course the extensive lung changes may account for a morbidity and mortality rate higher than that usual in patients undergoing similar surgery for bronchogenic carcinoma

Most of the 26 patients fell into the typical adenoma group Mitotic figures and variation in size shape and staining characteristics of individual cells were uncommon although about one third had local extension Only two had regional lymph node metastases and none showed distal blood stream spread Changes possibly representing mixed tumor were found in only three patients Heterotopic bone

(4) J Thorac Surg 21 535 543 May 1951

formation with osteoid tissue appeared in all of these and epithelial pearls were present in one Fourteen tumors were well encapsulated and showed no sign departing from benign neoplasm in the constituent cells In addition the only patient in whom bronchoscopic removal was the definitive form of treatment had survived nine years with no sign of recurrence Approximately 20% had large extrabronchial extension and in these as well as in a group with microscopic evidence of malignant change any attempt at local endobronchial removal would be doomed to failure

This neoplasm may be rightly termed an adenoma and primarily represents a pathologically benign lesion with a definite potentiality toward malignant degeneration Some limited lung resection apparently is the surgical choice The extent of pulmonary resection indicated can only be determined at thoracotomy If the mediastinal lymph nodes are clinically involved pneumonectomy is the only treatment of value regardless of the tumor s actual location Pneumonectomy also becomes necessary if the adenoma involves the main bronchus For lesions in more distal bronchi with no evidence of glandular metastases lobectomy is the choice Not one of the lobectomy patients has so far died of his disease and some have survived for many years

Dysgerminoma of Ovary with Associated Tuberculoid Reaction in Lungs and Lymph Nodes is reported by Lewis R Weintraub Philip Rosenblatt and Leonard Brandman[5] (Jewish Hosp Brooklyn)

Woman 78 had had severe pain in the lower abdomen and back nausea and anorexia for a month Except for slight dysmenorrhea menstrual history was not unusual The menopause took place at 50 She had been married but never pregnant Examination revealed a pelvic mass the chest was clear At laparotomy an extensive inoperable tumor was found in the pelvis fixing and obliterating all viscera After operation she did poorly and died in a month

Autopsy revealed several firm nodular implants on the pericardium and the peritoneum was studded with small white nodules In the lower abdomen and pelvis was a large firm rubbery pink gray white mass 20 cm in diameter Microscopically no normal ovarian tissue could be recognized Instead there was tumor composed of large round oval and polygonal cells with homogeneous pink staining cytoplasm The cells themselves varied

(5) Am J Obst & Gyn 61 1167 1170 May 1951

in size and occasional giant cells were seen Mitotic figures were present in some places Scattered throughout the lungs in regular fashion were collections of lymphocytes and peculiar giant cells of varying configuration In places the giant and lymphoid cells formed focal accumulations resembling granulomatous formation In one para aortic node was a nest of tumor similar to that of the ovarian region but the normal architecture of this node was maintained In another para aortic node normal architecture was seen only at the periphery the rest was largely replaced by broad bands of hyalinized fibrous connective tissue Scattered throughout were multinucleated giant cells and diffuse collections of round cells Small foci of necrosis were also seen but no tumor could be recognized Sections from a tracheobronchial lymph node revealed a picture intermediate between the above described nodes Microscopic preparations of other organs disclosed no unusual features other than tumor metastases and congestion

This is the oldest patient in whom an ovarian dysgerminoma has been reported the oldest previously reported being 52 Tuberculoid reaction in the lungs and lymph nodes is unusual no other case having been reported with this reaction in organs distant from the ovary

Primary Carcinoma of Peripheral Bronchi Cyril Raeburn[6] (London) studied the site and incidence of small primary bronchial carcinomas by examining lungs obtained at 400 autopsies on persons of average age 62 2 Lungs that appeared free from cancer either before or after fixation were cut into slices about 0 5 cm thick and any areas that looked or felt suspicious were taken for section When an obvious primary bronchial carcinoma was present the macroscopic pattern of growth was noted There were 15 gross peripheral primary growths 4 minute peripheral primary growths (3 of which were not over 2 mm in diameter) and 28 carcinomas of uncertain anatomic site Both gross and minute peripheral primary lesions were commoner than supposed the two together comprising 39 5% of all bronchial carcinomas In one case there were numerous oat cell secondary lesions but the primary lesion could not be found The early pleomorphism shown in two of the minute growths suggests that they originated either from bronchi distorted by inflammation or from associated mucous glands

Of the gross peripheral primary growths two each 34 cm in diameter were of interest because the first lesion seen

(6) Lancet 474 476 Sept 15 1951

at autopsy was a small plaque about 0 5 cm in diameter in the main bronchus A leash of permeated lymphatics con nected the intrapulmonary mass and the bronchial nodule and extended along and around the outer aspect of the main bronchus The lesion in the bronchus was likely secondary to the growth in the periphery of the lung If the primary growths had been smaller and had been missed on sectioning the lungs these small carcinomas in the main bronchi would have been accepted as primary growths The 15 gross periph eral primary growths either were isolated masses in the lung parenchyma or were connected with a lobar bronchus entirely by lymphatic permeation

Trachea and main bronchi are histologically identical yet carcinomas of the trachea account for but 0 4% of all car cinomas of the respiratory tract below the larynx The intra pulmonary bronchi lack the cough reflex and undergo a pro gressive simplification of structure in the respiratory bronchi ole the epithelium becomes cubical and nonciliated It is in *such small bronchi especially when distorted by inflammation* that an external carcinogen would be expected to exert its most prolonged effect rather than in the larger bronchi More over the smaller bronchi respond to chronic inflammatory proce ses not as a rule by transitional cell or squamous cell metaplasia but by the tubular and papillary cubical cell adenomatous proliferation which may often be seen in areas of pulmonary fibrosis From these potentially pleo morphic structures and associated mucous glands the initially pleomorphic minute carcinomas may arise Such carcinomas are relatively common and found at about 1% of all autopsies on adults in a hospital population If carcinoma arises in a random manner the incidence in each lung should correspond to the relative weights of the lungs This has been found to be true in over 2 000 collected cases of lung carcinomas In 649 cases lobar distribution corresponded closely with the relative weights of the lobes Thus there is a direct relation between tumor incidence and mass of lung parenchyma

There is sufficient evidence for regarding most bronchial carcinomas as peripheral in origin If this is true no bronchial carcinoma will be detected by bronchoscopy until lymphatic permeation into the lobar bronchus has occurred

[This is an important conception if verified by further study As the

author indicates it would have many implications diagnostically since we could not expect to diagnose many carcinomas in the early phase —Ed]

Terminal Bronchiolar or "Alveolar Cell" Cancer of Lung Report of 33 Cases is presented by William L Watson and Robert R Smith[7] (Memorial Hosp New York City) Pain and cough were the commonest symptoms Bloody sputum

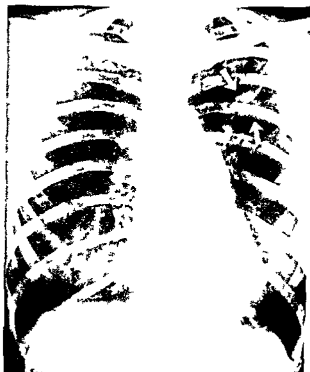


Fig 39 —C cums b d tumo l ft pp lobe (Cou t y f Wat o W L and Sm th R R J A M A 147 7 13 S pt 1 1951)

was noted in nine cases but frank hemoptysis in only one Average duration of symptoms before hospitalization was four months In 15% of cases the disease was asymptomatic and discovered by routine chest x rays Clinical diagnosis in 22 cases was *terminal bronchiolar carcinoma* cytologic studies of sputum established the diagnosis in 5 aspiration biopsies of lung masses in 5 thoracotomy with biopsy in 8

(7) J A M A 147 7 13 S pt. 1 1951

and biopsy of a peripheral lymph node in 4 In five cases clinical and laboratory data indicated a malignant lung tumor but the exact diagnosis was made only at autopsy

Roentgen diagnosis of malignant lung tumor was made in only 65% of cases In one instance x ray studies were negative but exploratory thoracotomy revealed a nonresectable tumor The commonest finding was a single peripherally located circular area of increased density usually 2-4 cm in diameter (Fig 39) This nodule seemed to differ from the usual metastatic nodule in that it was more irregular slightly larger less homogeneous less sharply outlined and less dense Seven patients had multiple nodules and the disease was bilateral in several instances Roentgenographically the disease might be confused with pneumoconiosis miliary tuberculosis or metastatic cancer There was however no evidence of fibrosis and the nodules seemed to coalesce to form infiltrative masses Cytologic studies were made in 15 cases 6 specimens were reported as Papanicolaou class V (conclusive proof of cancer) 3 as class IV (positive for cancer) and 3 others as class III (strongly suggestive of cancer) In one case in which pneumonectomy was done class V sputum was the only positive evidence on which the decision to operate was based Papanicolaou has noted that this tumor exfoliates profusely and yields abundant characteristic material

The only effective treatment is surgical excision Two patients operated on before 1945 were well after five years one had lobectomy and one simple excision of the mass Both were in the early stage in which a limited procedure was sufficient to eradicate the disease Nine patients with more extensive disease required pneumonectomy Four were dead and five were living six months to two years after operation Another means of treatment that requires more study and trial is a combination of surgery and irradiation in this procedure the primary bulk of diseased tissue is excised and interstitial radon in the form of gold seeds is placed in the remaining inoperable cancer External irradiation can then be more accurately directed to the well marked residual cancer

Carcinoma of Bronchus Clinical and Pathologic Survey of 866 Cases is reported by C C Bryson (Archway Hosp) and H Spencer[8] (St Thomas s Hosp London) The propor

(8) Q t J M d 20 173 186 Ap 1 1951

tion of bronchial carcinoma to all forms of malignant disease found at autopsy was nearly the same in the triennia 1936-38 (25%) as in 1945 (27 1%) Hence the reputed increase in incidence of these growths seems more apparent than real The great preponderance of the disease in men was again confirmed the proportion of male to female patients being almost 6 1 (Fig 40) Peak incidence in women was at a slightly later age than in men Occupational factors were not related to incidence

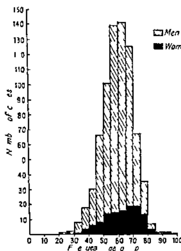
SYMPTOMS IN ORDER OF FREQUENCY

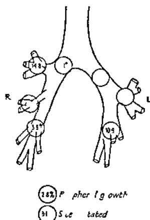
Men (743 Cases)		Women (123 Cases)	
Cough	52 6%	Cough	48.8%
Weight loss	35 1%	Dyspnea	3? 0%
Dyspnea	33 1%	Weight loss	30 9%
Chest pain	29 6%	Chest pain	28.5%
Hemoptysis	26 4%	Headache vertigo fits paresis	19 5%
Headache vertigo fits paresis	14 6%	Hemoptysis	8 9%
Abdominal pain	9 0%	Shoulder pain	6.5%
Pain in back of legs	7 3%	Dysphagia	6 5%
Influenza	5 0%	Enlargement of lymph nodes skin nodules	5 ?%
Vomiting	3 4%	Influenza	5 7%
Shoulder pain	3 1%	Vomiting	4 1%
Hoarseness loss of voice	3 0%	Abdominal pain	4 1%
Dysphagia	2 8%	Medical emergencies	2 4%
Enlargement of lymph nodes skin nodules	2 7%	Hoarseness loss of voice	0 8%
Medical emergencies	1 5%		
Jaundice	1 2%		

but available information was inadequate The high proportion of men with long history of cough and chronic bronchitis may be important for these symptoms may have been related to heavy smoking a possible factor in the etiology of bronchial carcinoma Other previous diseases of the chest including tuberculosis were not significant

Symptoms and signs were extremely variable (table) but the combination of cough dyspnea and chest pain was so constant as to suggest that neglect of this triad of symptoms in persons over 40 might prevent discovery of many early cases of bronchial carcinoma Small and often repeated hemoptysis observed much more commonly in men than in women may have been related to the greater frequency of chronic bronchitis in men Sites of origin of the tumor differed little in the two lungs (Fig 41) The small proportion of peripheral neoplasms conformed to the usual observations of other

authors Minute primary growths in the lungs with wide spread and massive secondary deposits in other organs may render diagnosis of the primary tumor extremely difficult but histologic examination of an accessible secondary deposit often leaves little doubt as to the primary site No organ is exempt from metastasis The liver was involved oftener than any other organ and sometimes the growth was so





Fg 40—I d f b h l oma
Fg 41—D t b t n f p mary g wth n b on h l t ee
(Cou te y f B y C C nd Sp H Q t J M d 20 173 186 Ap l 1951)

extensive that liver enlargement and terminal jaundice due to intrahepatic biliary obstruction overshadowed all other symptoms and signs

Tumors were divided into five histologic types but con siderable pleomorphism was found Oat cell carcinoma showed less variation in structure in both primary and metastatic growths and accounted for 36% of all bronchial carcinomas Adenocarcinomas despite their more differenti ated character were highly malignant Prognosis in all the varieties of growth was uniformly bad but survival was longest in the metaplastic squamous cell group and these growths gave rise to fewer metastases The latter group

may account for some of the slowly growing tumors which remain symptomless for years Average age of incidence varied little

Failure of ordinary x ray examination to reveal a growth in the chest was not surprising in view of the secondary pathologic lung changes which masked the underlying causative lesion *A negative radiologic report should not engender* a feeling of security Bronchoscopy and sputum examination for malignant cells were indispensable when doubt existed as to possible presence of a growth Therapeutic results were uniformly disappointing and the number of cases suitable for extirpative surgery was small Deep x ray therapy offered the best means of prolonging life for a few weeks

Factors Responsible for Failure of Cytologic Examination in Cases of Bronchogenic Carcinoma Cytologic examination of the sputum or bronchial secretions was performed before operation in 184 cases of bronchogenic carcinoma *In 133* it disclosed carcinoma cells in the remaining 51 it failed to disclose such cells The cytologic slides and surgical specimens *from these 51 cases were studied by Donald K Buffmire* and John R McDonald[9] (Mayo Clinic) Histologic type included adenocarcinoma in 21 cases large cell carcinoma in 12 and squamous carcinoma in 10 In the 21 cases of adenocarcinoma it was difficult and at times impossible to decide whether the pulmonary lesion was primary or metastatic Squamous carcinoma the commonest type of bronchogenic carcinoma tends to involve the larger bronchi Both large cell carcinomas and adenocarcinomas have a tendency to develop at the periphery of the lung They often occur as a *small nodule which cannot be found to communicate with a* bronchus Metastasis in the lung usually occurs by way of the blood stream and metastatic implantation occurs outside the bronchus Ulceration is a late manifestation of metastatic tumors of the lung In 28 of the 51 cases in which cytologic examination failed to disclose carcinoma cells the tumor either involved a tertiary bronchus or was situated just beneath the pleura No communication between the tumor and bronchial tree could be found in 16

Bronchoscopy had been performed on 47 patients Results were normal in *35 biopsy disclosed carcinoma in 5 a lesion*

(9) S Cli North Ame a 31 1191 1197 A gu t 1951

was visible in 4 but biopsy did not disclose carcinoma de formity of the bronchus was present in 2 and blood could been seen coming from a main bronchus in 1 The bronchus was completely obstructed in 18 In five of these cytologic examination was inadequate (less than three smears of sputum or less than two smears of sputum and one of bronchial se cretion examined) The bronchus was partially obstructed in three patients Slides were unsatisfactory for cytologic ex amination in two cases In one additional case the smears contained so many erythrocytes that the normal nonmalignant cells could not be identified In six cases cytologic examination disclosed atypical cells but the number of such cells was not large enough to warrant positive diagnosis of carcinoma It was impossible to determine the factors responsible for the normal cytologic observations in five cases In all of these the tumor involved a large bronchus adequate material was available for examination and there was no evidence of bronchial obstruction

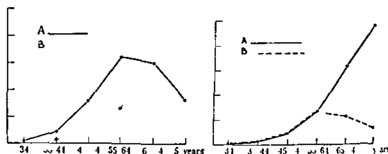
Age Curve in Lung Cancer R Korteweg[1] (Amsterdam) points out that most curves indicating cancer death rates per million living in the different age groups rise continuously with advancing age The steepness of the rise generally falls off with increasing age and declines in some instances in the oldest age group This holds true not only for total cancer mortality but for cancer of various organs This is true in lung cancer In 1949 in The Netherlands the age curve for lung cancer in males began to decline at an age lower than is ever seen in other cancers In 1945 in England and Wales this exception to the rule was still more prominent (Fig 42)

Among those under 35 lung cancer has not increased greatly but in all the older age groups increase has been large and continuous and even in 1945 showed no signs of slowing Cancer develops only after a long period of prepara tion which in most cases can be counted in decades Those who at 80 contract cancer do so partly because of an earlier tendency to cancer It would be wrong therefore to compare in this respect persons who in 1945 were 80 with persons who in the same year were 70 This comparison should be made with those who 10 years earlier belonged to that age group The lung cancer age curve constructed according to

(1) Brit J C 5 1 27 M b 1951

this principle does not differ in any way from other cancer age curves The so called age curve for lung cancer in males with its decline at a relatively early age is an illusion The same objection can be made to a greater or less extent to all other age curves constructed in this way It is only by chance that most of these do not diverge far from reality as most cancer death rates have not altered much in the course of the last decades

Up to age group 55 64 the shape of the illusionary age curve is about normal only after that does the sharp decline



Fg 4 (left)—Age curves for ca er n mal s E gl I d W le (1945) *A* l ng n (5 941) *B* ca all oth s t s (30 835)
Fg 43 (r ght)—Bala ce of l g n er m rtal ty in males Engl nd nd Wal s (1945) *A* l g c n g c r ft co ect o *B* p e d l g ca r ↓ c
(Co te y of Kort w g R B t J C c 5 21 27 Ma h 1951)

begin In 1945 in England and Wales in males under 65 deaths from lung cancer were 33 8% of those from all cancers except lung cancer Apparently if the lung cancer age curve in 1945 had its real shape the number of all deaths from lung cancer would have been 33 8% of those from all cancers except lung cancer i e $(33\,8/100) \times 30\,835 = 10\,422$ which is 4 481 more than actually died from lung cancer In 1945 therefore the ceiling of lung cancer mortality in males corresponded to a level of 10 422 (Fig 43) If the danger offered by environmental factors promoting lung cancer were now suddenly to become stationary the number of lung cancer deaths would probably still go on increasing to about double the present figure

Pulmonary Tuberculosis Bronchiectasis and Calcification as Re ted to Bronchogenic Carcinoma In 23 cases of bronchogenic carcinoma found at autopsy operation or biopsy C

Eugene Woodruff and Hector C Nahas (Northville Mich) noted 12 squamous cell type tumors sufficiently differentiated to form epithelial pearls in either the right or left upper lobe All but 1 were associated with large calcified foci in the same lobe or in the adjacent tracheobronchial lymph nodes and all but 2 showed no associated active tuberculosis Lung tumors of other types had quite different anatomic changes

Failure to find tubercle bacilli in the sputum smears of any patient with squamous cell carcinoma of the lung seemed surprising particularly since obvious central excavation of the tumor was present in most cases and most of the men had been exposed to open cases of tuberculosis during their stay in the sanatorium However the central cavity of a tumor of this type was lined by debris from squamous epithelial cells and squamous epithelium is notoriously resistant to infection with tubercle bacilli Bronchiectasis is a common residuum of tuberculous infection and in an area of old bronchiectasis the normal columnar epithelium of the bronchus is frequently transformed into epithelium of the stratified squamous variety This type of epithelial metaplasia the result of chronic irritation usually precedes development of squamous cell carcinoma in any of the viscera Bronchiectasis has long been recognized as a common observation in primary carcinoma of the lung but has usually been considered a result of the bronchial obstruction caused by the tumor The finding of calcified lymph nodes closely associated with bronchogenic carcinoma means that in these cases it is possible if not probable that bronchiectasis preceded tumor development

Agenesis of Right Lung Louis B Thomas and Edward A Boyden[3] (Univ of Minnesota) report three cases

Case 1—Boy 2 had aspirated a kernel of corn several hours previously and was markedly dyspneic and somewhat disoriented Expiration was prolonged and wheezy with bilateral interco tal retraction on inspiration The thorax was symmetrical Breath sounds were heard over the left ide of the chest but not over the anterior two third of the right side No heart sounds were heard Birth growth and development had been normal Only previous illness was bronchiti at 1/ years Chest x rays taken shortly after

( ) Am R T be 64 6 0 6 9 D mb 19 1
(3) S g y 31 429 435 M b 1952

aspiration of the kernel were reported to show collapse of the right lung (Fig 44) Bronchoscopy revealed the kernel in a bronchus leading off to the right subsequently identified as the left middle bronchus The kernel was dislodged but fell into a bronchus leading to the left—the left lower lobe bronchus At this point the child stopped breathing and died

Autopsy showed pronounced displacement and rotation of the mediastinum and its structures The heart lay in the right thorax



F g 44 —Ch t film h w g d by l ft pl u l s H t d ty d s pl c d t ght s h dly g ble (Cou te y of Th m L B and Boyde E A Su ge y 31 4 9 435 M h 195)

and an enlarged left lung filled the left thorax and extended anteriorly across the midline to the right The somewhat flattened lung bore little superficial resemblance to a left lung but on dissection was found to have three lobes It could be classified as belonging to type III lungs having a cleft left upper lobe No right lung or right main stem bronchus could be found The upper portion of the right thorax was filled by the great vessels and a moderate sized thymus No pleural space was found on the right The heart arch of the aorta and its vessels were normal except for displaced position The normal pulmonary artery sent branches into the left lung only A single pulmonary vein from the left lung entered the left atrium at the midpoint of its posterior wall The trachea was in the midline and was normal as was the larynx A kernel of corn wa found in the bronchus of the left inferior lobe No

Fig 45—A [illegible] w f th [illegible] hed l ft l g n Case 2 H rt b been d ba k to pose pe d d d l ted or na y [illegible] (w th t ppe d d l ft su or [illegible] ca) d ou se f l ft pulmona y th gh floo of oro ry na. Pulmo ry [illegible] l b dd l ft l m soo t h floo f nary B d t l f l ft b h l t d ectop p lmon y rt ry Ca 2 N t that a te y pl t uppe lobe b on hu C t w f l ft l g Case 3 Not back f lobe typ l pos on f l ft p lm ry tery beh d l ft b on h s, n b b n t h d l g d d ct t omp y g tat u f rta (Court y f Th m L B d B yd E A S g ry 31 429 435 M h 1952)

gross anomalies were evident except for agenesis of the right lung and absence of the right pleura

CASE 2—Twin girl aged 16 days had agenesis of the right lung diagnosed roentgenographically and died after operation for tracheoesophageal fistula The left lung was three lobed and belonged to type IV having a cleft left upper lobe associated with an ectopic left pulmonary artery (Fig 45 A and B)

CASE 3—Full term boy never breathed beyond emitting a few

aspiration of the kernel were reported to show collapse of the right lung (Fig 44) Bronchoscopy revealed the kernel in a bronchus leading off to the right subsequently identified as the left middle bronchus The kernel was dislodged but fell into a bronchus *leading to the left*—the left lower lobe bronchus At this point the child stopped breathing and died

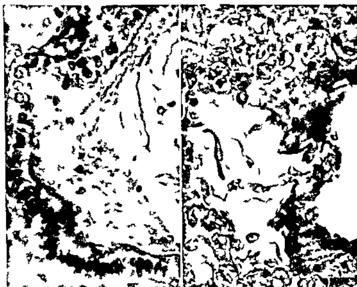
Autopsy showed pronounced displacement and rotation of the mediastinum and its structures The heart lay in the right thorax



Fig 44—Chest film sh w ng a e c ed by l ft pl ural s c H a t d ns ty d s pla d to ight h dly e og zable (Cou te y of Thomas L B nd Boyden E A S rge y 31 4 9 435 Ma h 1952)

and an enlarged left lung filled the left thorax and extended anteriorly across the midline to the right The somewhat flattened lung bore little superficial resemblance to a left lung but on dissection was found to have three lobes It could be classified as belonging to type III lungs having a cleft left upper lobe No right lung or right main stem bronchus could be found The upper portion of the right thorax was filled by the great vessels and a moderate sized thymus No pleural space was found on the right The heart arch of the aorta and its vessels were normal except for displaced position The normal pulmonary artery sent branches into the left lung only A single pulmonary vein from the left lung entered the left atrium at the midpoint of its posterior wall The trachea was in the midline and was normal as was the larynx A kernel of corn was found in the bronchus of the left inferior lobe No

difference in microscopic appearance between hyaline mem branes formed of amniotic fluid which is aspirated before this rise takes place and those formed afterward The membranes were independent of pulmonary hemorrhage edema or in flammation and were not formed of degenerated airway epi thelium The common observation that infants who have aspirated amniotic sac contents often have a brief period of



Fg 46 (l ft) —A i ph l m mb ov g nt t b on h l p th l m w th q m ll l m p t d m mb d ly g b tw m m b d p th l m H t yl d d f m × 550
Fg 47 (ght) —H l m mb w h q m ll ly g b tw m m b d l l w ll H m t l d d f m × 700
(C t y f Bly t i W t l P d t 8 5 1 J ly 19 1)

relative well being before development of respiratory distress leading to death is best explained by progressive atelectasis resulting from these membranes This phenomenon is de scribed as a typical clinical feature of congenital alveolar dysplasia although the mechanism is difficult to understand if the lungs are truly unexpandable no instance of this condition was found in 509 cases

After 0 5 2 cc human amniotic sac contents was injected intratracheally into white rats lightly anesthetized with

spasmodic gasps Autopsy revealed an incompletely divided left lung with atypical branching of the bronchial tree a nubbin at the site of bifurcation of the trachea (which may represent a right bronchial bud) a retrobronchial left pulmonary artery coarctation of the aorta (Fig 45 C) a supernumerary digit and hydronephrosis due to a stricture of the ureter just below the ureteropelvic junction

These three cases are apparently the first in which the segmental anatomy of the single remaining lung has been worked out In each there were striking deviations in the *bronchovascular patterns of the left lung* These with associated congenital anomalies suggest interference with normal developmental processes beginning at the end of the first lunar month Agenesis of the lung, ocular cardiovascular and urogenital anomalies have been produced in rats by deficiency of vitamin A in the maternal diet in these experiments the chemistry of development has been disturbed In man this may be accomplished hereditarily by a defective gene or *environmentally by any agent that imposes on the embryo* an appropriate nutritional deficiency

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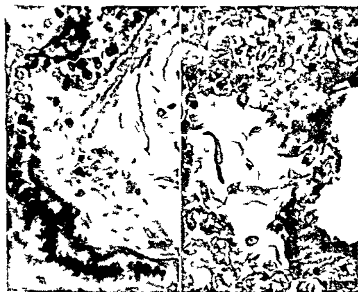
MISCELLANEOUS

Pulmonary Hyaline Membranes in Newborn Infants Statistical, Morphologic and Experimental Study of Their Nature, Occurrence and Significance Wilhelm Blystad Benjamin H Landing and Clement A Smith[4] (Children s Med Center Boston) analyzed histories and autopsy material of 509 newborn infants and found that pulmonary hyaline membranes (Figs 46 and 47) occurred most commonly in premature infants and in more mature infants with history of a complication of pregnancy labor or delivery capable of causing fetal anoxia They were not seen in stillborn infants or in infants living less than one hour They seemed to cause atelectasis by blocking the mouth of alveoli and to be a major cause of death in the neonatal period

Studies on vernix meconium and amniotic fluid indicated that these hyaline membranes were formed not of vernix or meconium but of the concentrated protein of aspirated amniotic fluid Rise in squamous cell content of amniotic fluid during the third trimester of pregnancy may explain the

(4) P diatr 8 5 21 J ly 1951

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F g 47 (ght) —H l m mb w th q m ll ly g b tw m m b n d l l w ll H m t yl n d d f om × 00
(C rt y t Bly t d W t l P d t 8 5 21 J ly 1951)

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After 0 5 2 cc human amniotic sac contents was injected intratracheally into white rats lightly anesthetized with

ether hyaline pulmonary membranes were not seen in sections of any lung On the other hand when 15 20 cc amniotic sac fluid was injected *intratracheally* in 1 cc amounts into excised adult guinea pig and mouse lungs while the lungs were alternately expanded and contracted for one hour amniotic squamous cells were seen in small clusters in alveoli or in membrane formation around the walls of alveoli and thin *hyaline acidophilic membranes in some alveoli* Thus with sufficient amniotic fluid introduced into the airway and respiration continued for a sufficient time after injection pulmonary membranes *similar to those seen in* newborn human infants can be produced

[It has not been demonstrated that presence of these hyaline membranes in the lungs will interfere with expansion It seems probable that *aspirated material in the lungs of infants might create some exudative* reaction and provide a bed for infection —Ed]

Green Sputum *A John Robertson*[5] *(Royal Infirm Liverpool)* studied the absorption spectrum of the green pigment in 50 samples of sputum collected from patients with bronchiectasis or lung abscess Samples were centrifuged the greenish upper layers were emulsified with chloroform and centrifuged *for a long time In this way* a greenish solution clear enough for spectrophotometry was obtained It could be concentrated by boiling under low pressure or by dialysis Absorption curves looked *similar to those of verdoperoxidase* and the criteria for spectroscopically establishing that this was the substance were fulfilled Further purification finally produced a solution of fairly pure verdoperoxidase which gave an intense blue reaction with guaiacum and hydrogen peroxide

When the granulocytes disintegrate verdoperoxidase is set free and if there is failure to excrete this enzyme the purulent material becomes visibly green This happens whenever there is stagnation which is especially found in disease of the bronchial wall For example during the night the bronchiectatic *patient may not cough much and by morning* the sputum may be green but once this has gone the purulent material may revert to its normal color unless there is continued difficulty with expectoration In a lung abscess there is destruction of leukocytes with failure to excrete any enzyme hence a *green color may be found* when the abscess is coughed up

(5) La et 1 1215 Ja 5 1952

DISEASES OF THE PLEURA

Diagnostic Value of Glucose Content of Serous Pleural Effusions W L Calnan B J O Winfield Mary F Crowley and Arnold Bloom[6] (Whittington Hosp) examined 61 pa tients 25 of whom were tuberculous 30 nontuberculous and 6 undiagnosed The term undiagnosed was used because of the lack of bacteriologic confirmation of the tuberculous origin of the effusion and of any other cause Pleural fluid was collected two hours after the patient s last meal and concomitant blood sugars were taken in many cases Fluoride was used to prevent glycolysis and the glucose was estimated by Hagedorn and Jensen s method

No correlation between the blood and pleural fluid glucose levels was evident All 30 nontuberculous pleural effusions had a glucose level of over 60 mg /100 ml and in 24 of these it was over 100 mg /100 ml Thirteen of the 25 tuberculous patients had glucose values below 60 mg./100 ml of the other 12 1 also had amyloid disease and another was diabetic with a glucose level of 220 mg./100 ml in the pleural effusion In the six undiagnosed cases glucose levels ranged from 62 to 96 mg /100 ml four were considered clinically and radio logically of tuberculous postprimary type but bacteriologic confirmation was lacking Eight tuberculous and seven nontu berculous patients had glucose levels between 60 and 100 mg /100 ml Glucose values in the six undiagnosed cases would therefore be valueless in determining etiology of the effusion

Radioactive Isotopes in Palliative Management of Car cinomatosis of Pleura Edward M Kent and Campbell Moses[7] (Univ of Pittsburgh) treated 19 patients with established carcinomatosis of the pleura and rapidly forming intract able pleural effusion with radioactive iodine (I^{131}) radioactive gold (Au^{198}) and I^{131} tagged human albumin (in one case) An arbitrary dosage of 10 mc I^{131} was chosen initially but dosage was later increased to as much as 30 mc I^{131} was transferred to a 50 100 ml bottle the pleural effusion aspirated

(6) B t M J 1 1239 1 40 J 2 1951
(7) J Th S g 2 503 516 Nov mb 1951

as completely as possible the I^{131} containing bottle filled with pleural fluid and the I^{131} containing pleural fluid reinjected into the pleural cavity

Of the 14 patients with a neoplasm of bronchogenic origin 3 died too soon after therapy for evaluation of results However pleural effusion was not a factor in the death of any of them and in each it appeared to be checked or greatly retarded In three patients results were fair fluid reaccumulated in sufficient quantity to require aspiration at least once after the immediate post therapy interval In eight effusion was promptly and completely checked In all four patients with primary carcinoma in a breast and in one whose primary lesion was myxofibrosarcoma of the anterior abdominal wall results were good although two continued to have small amounts of pleural fluid until death No toxic manifestations due to the isotopes were noted

Pulmonary Tuberculosis Following Pleuritis A Wernli Haessig[8] (Zurich) reports six cases of pleuritis in which pulmonary tuberculosis was discovered on follow up roentgen examinations The patients had remained asymptomatic and sedimentation rates were not increased All patients with pleuritis erythema nodosum or primary tuberculosis lesions should be examined by fluoroscopy in the 1st 3d 6th and 10th months after the initial examination and twice yearly thereafter for 3 years Films should be obtained in the 3d and 10th months and then once a year they should be taken whenever any suspicion of infiltration exists and repeated at monthly intervals until it is determined whether the lesion is progressing or is stationary Sanatorium residence often may be necessary for such rigid follow up The risk of pulmonary tuberculosis diminishes with time and becomes negligible if two years have elapsed after pleuritis without development of any postprimary lesions In cases in which tuberculosis developed after 10 years roentgen follow up either had not been done or the minimal changes that had appeared were considered benign because of absence of clinical signs and symptoms

Of 30 reported cases in which streptomycin therapy was used tuberculosis developed within two years after pleuritis in only 10% The number of cases is small and although

(8) S hw med W h sch 31 1080 1085 N 3 1951

results seem encouraging streptomycin therapy remains to be evaluated

Prognosis of Tuberculous Pleurisy Comparative Investigation with That of Scheel and Føien. Simon Frostad[9] (Molde Norway) discusses 720 of 909 cases of pleurisy which developed in 1926-35 in formerly healthy persons none of whom had had tuberculosis They were followed 3 17 years Patients in whom the process was of known nontuberculous etiology were eliminated from the study In over half the patients onset was between ages 16 and 25 Most cases began in the period of February to June

Of the 720 patients 148 (20 6%) became tuberculous 118 had tuberculosis of the lungs and 6 of these also had tuberculosis in other organs Sixty six patients died of tuberculosis 7 of tuberculous meningitis or solitary tuberculoma in the brain and 10 of miliary tuberculosis Two patients had tuberculous peritonitis six another type of pleurisy complicated by pericarditis one tuberculosis of the kidney four tuberculosis of the bones Both morbidity and mortality from tuberculosis increased with age Morbidity was 10 6% in patients under 15 and increased to 19 6% in the age group of 16-25 and to 23 1% in the 26-40 group In those over 40 it increased up to 40% although there were few patients in this age group this corresponds with the less favorable prognosis for the higher age groups found by other authors Mortality distribution followed the same pattern Mortality and morbidity were the same in males and females

Most cases of tuberculosis developed within five years after pleurisy (120 of the 148 cases) In the same period 55 of the 66 deaths due to tuberculosis occurred In the first year 58 cases of tuberculosis appeared and 24 patients died Extrapulmonary tuberculosis was in a great degree responsible for the high morbidity and mortality Even 12 years after onset of pleurisy however cases of tuberculosis appeared and even after 13 years there were deaths Allowance must be made for the uncertainty in determining the exact date of onset of tuberculosis In another series of 282 patients with tuberculosis all had had pleurisy previously Most cases of pleurisy had developed at age 16-25 and in 231 patients tuberculosis developed during the same period

(9) A t m d sc d 39 341 357 1951

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membrane trypsin was definitely effective The pleura di rectly inspected in five cases was clean and glistening even when greatly thickened in one which showed complete calcification of the cavity wall the calcium plaques were found at decortication to be loosened from the wall and lying free in the space Viscosity of the empyema fluid was de creased in all 17 cases This change was rapid and impressive Sterilization of the space was an unexpected development It was originally planned to follow trypsin treatment with penicillin or streptomycin therapy In 13 of the 17 cases smears and cultures were positive at the beginning of treat ment and became ne ative in 12 after 3 60 days (average about 10 days) Conversion did not occur in one case—the only complete failure Trypsin was most effective in non tuberculous empyema with re expansion in four of the five cases with trypsin alone In the fifth case of six months duration decortication was necessary

A great decrease in toxicity was manifested in all cases Daily temperatures in general decreased Appetite and general sense of well being increa ed Decrease in toxicity is of the utmost benefit in preparing patients for surgery

Treatment of Primary Serofibrinous Pleurisy with Com plete Evacuation of Exudate and Injection of Streptomycin into Pleural Cavity is reported by E Danopoulos and K Melissinos (Univ of Athens) in 47 patients aged 10 47 over half were under 20 Drug injection was 1 Gm in 20 cc saline Treatment was within the first 10 days of onset in 17 cases between 10 and 20 days in 19 and after 20 days in 11 In 23 of 27 patients who required only a single intrapleural injection general signs of the disease regressed in one to six days the rest still had fever for some time but other toxic manifestations (sweats anorexia) disappeared rapidly In 16 other patients a second pleural tap with injection of streptomycin was performed after two to eight days Toxic manifestations disappeared in all 16 but 4 still had slight fever Sedimentation rate diminished slowly in all patients despite good clinical improvement in some an elevation was ob served due perhaps to fibrin absorption In the other four patients seen one to three months after onset of the disease three to five treatments and streptomycin intramuscularly

(2) W med. W b h 63 333 334 M y 4 1951

Most cases of pulmonary tuberculosis were found in the first year after pleurisy but in the subsequent nine years there was about the same distribution of tuberculous cases as in the other series Later the figures were considerably lower but cases of tuberculosis continued to develop up to about 30 years About 16% of the cases developed after 10 years had passed

Annual average morbidity and mortality were 5 and 2 05% respectively in Scheel and Føien s series covering the period 1916 25 whereas they were 2 7 and 1 2% in this series

[The prognostic significance of tuberculous pleurisy is now rather generally recognized It should be taken as a sign of active disease in the lung even though the lesion is so small as to be invisible in the roentgenogram Prompt treatment at this time will do much to avoid progression of the disease Such patients particularly if they are young should have prolonged rest treatment which averages about a year—Ed]

Use of Trypsin in Chest Disease L C Roettig Howard G Reiser William Habeeb and Louis Mark[1] (Columbus O) present results of trypsin therapy in 17 cases of empyema Since trypsin will only lyse dead tissue and will not attack a living cell it is relatively safe for administration as opposed to the proteolytic streptococcus enzymes against which the body has no antienzyme Pure crystalline trypsin in 0 5% phosphate buffer solution is instilled intrapleurally The patient is usually prepared with an antihistamine (20 mg benadryl® intravenously or 50 mg histadyl orally) trypsin is administered and the patient instructed to turn frequently in bed and sit up from time to time Afterward an antihistamine is given orally On subsequent treatments aspiration saline lavage and trypsin instillation are carried out

In the first two cases there were complete re expansion of lungs and healing of empyema with trypsin instillation and aspiration alone It seemed that trypsin might be a means of debriding expanding and sterilizing empyema by itself Subsequent experience proved that complete cure with trypsin alone can be expected only if the empyema is of less than six months duration before excessive scarring has occurred

On the basis of re expansion of the lung with trypsin alone results were satisfactory in 6 of the 17 cases The longest period empyema was present before treatment was six months From the standpoint of removal of the pyogenic

(1) Dis Chest 21 45 259 March 1952

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(1) D Ch t 1 245 259 M r h 1952

THE BLOOD
and BLOOD-FORMING ORGANS

WILLIAM B CASTLE M.D

were required therapy failed Age did not influence response

Five other patients received streptomycin intramuscularly In four who did not react to 3 12 injections a single intra pleural treatment caused exudate and other manifestations to disappear

[The local use of antibiotics in the pleura seems to be definitely beneficial in established tuberculous empyema but it is doubtful whether it should be used in this way in serofibrinous pleurisy If the patient requires specific treatment this had better be given by the usual routes Instillation of drugs in the pleura does not seem to have any advantages except when the fluid becomes thick and purulent —Ed]

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS AND SPECIAL TECHNICS

Studies with Inagglutinable Erythrocyte Counts III Kinetics of Erythrocyte Destruction in Human Beings Transfusion of biologically tagged erythrocytes and subsequent identification and enumeration of donor cells in the recipient s circulation by differential agglutination afford a valuable means of studying the fate of the donor s abnormal cells in a normal recipient or disappearance of normal cells in the diseased person Most such studies have however merely shown the time between transfusion and disappearance of the last detectable cells from the circulation

Utilizing this technic Raymond F Sheets Clinton D Janney Henry E Hamilton and Elmer L DeGowin[1] (State Univ of Iowa) studied destruction of normal erythrocytes in diseased persons and of defective erythrocytes in normal subjects Observations of others were confirmed that transfused normal cells disappear completely from the circulation of normal recipients in 120 $\pm$ 15 days and during their life span are lost at a constant rate conditioned by an aging factor Survival of defective transfused cells may be abnormally shortened because of premature aging A case is reported in which red cells from a subject with Cooley s trait completely disappeared from the circulation of a normal recipient in about 85 days Because the successive concentrations of donor s cells when plotted described a straight line they apparently had a uniform life span of 85 days an example of accelerated senescence at a constant rate

It was theorized that transfused red cells may be lost in other disorders by a destructive mechanism acting at random regardless of age in addition to the normal aging process

(1) J Cli In est. 30 1272 1286 N vember 1951

structive mechanism of constant rate in addition to normal aging It was uninfluenced by therapy with vitamin B_1 despite increase in patient s red cell production A similar explanation obtained when erythrocytes from a patient with severe lead poisoning were lo t from the circulation of a normal recipient

[The few observations by others have disclosed normal survival of normal red cells in pernicious anemia but a short survival of the patient s red cells in normal recipients —Ed]

Improved Technic of Bone Marrow Aspiration is described by Simon Propp (Albany Med College)

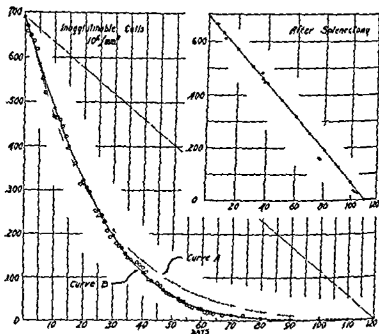
TECHNICS —If the patient is not overly apprehensive the sternum i punctured otherwise the iliac crest or vertebral spinous process may be chosen In infants under 2 a specimen of tibia marrow is usually taken The marrow aspiration needles used are either Osgood or Rosenthal 16 and 18 gauge shortened to 2 1 5 and 1 cm lengths from point to hub and fitted with stilets Sodium heparin olution (commercial diluted with neutral saline so that 1 cc contains 1 mg) is drawn aseptically into a 2 cc syringe to wet the interior and about 0 05 cc is left in the tip Using careful asepsis *and infiltration of skin subcutaneous tis ue and periosteum over the* body of the sternum the kin is pierced with a marrow aspiration needle and the needle advanced to the periosteum vertically in adults and at an acute angle in children The cortex is punctured by pressing and rotating the needle th stilet being held firm The marrow cavity may be entered abruptly or gradually Aspiration is tried as soon as the needle is fixed in bone Rotation of the needle repeated attempts at aspiration and use of a 10 cc syringe may be necessary The patient often notes a drawing sen ation when suction is exerted in the marrow space

The aspirated fluid resembles blood About 1 cc is obtained The needle is then removed with a careful rotating and pulling motion and a sterile dressing applied Marrow is sucked into the syringe and the barrel inverted 12 times and gently shaken to mix the marrow cells Four to six thin cover slip and two cresyl blue smears are made the latter by inverting cover slips with a drop of blood in the center on a cresyl blue stained slide The edges are sealed with petrolatum Cresyl blue slid s are prepared by placing a drop of brilliant cresyl blue solution (0 5 Gm powdered dye in 100 cc of 95% ethyl alcohol) on a glass side and spreading it evenly with a glass rod They are then air dried Cover slip marrow smears are covered with a methanol solution of Wright s stain for two minutes then distilled water is added in equal volume and allowed to remain for six minutes

The remaining material is ejected on a concave slide Marrow particles remaining in the syringe are removed and smears made of

(2) Blood 6 585 599 J ly 1951

Equations were derived to express the relations when the random destructive mechanism has a constant rate and also when its velocity increases during the experiment Splenectomy restored the rate of red cell loss to normal (Fig 48) Loss of



F g 48 — D sappeara e curv f tr nsfus d fresh norm l eryth ocyt lost by ra dom de t ct o w th re ng rate pl norm l agi g a d ab t on f random d st u t m h sm aft sple ctomy F sh g oup O e yth ocyt s f om a or mal dono w t sf ed nt a pati t w th po t rot ctr ho s of th l v r belonging to gr p A In ggl t nable ll counts (op rcle) fitt d only the first half f curv A lcul ted f u n equat on wh ch a um s co t t ate f and m de t uct or plu n mal g g A cl se fit f ob erved data wa bta n d w th curv B lculated the b sis f an equat on wh ch assume lo s f om n rmal aging plus andom d st uc ion at an s ng r te Ass mpt n of an inc easi g rate of ell d stru t n c re pond d well w th cl cal ob e at ons that the d s ea was be m g wo Aft r pl n tomy otte t a fus on of f sh ormal eryth ocyt su d n the r c pi t a mal m ne I et show n ggl t able ell ou ts (Lou te y f Sl e ts P F t l J Cl n Invest 30 1272 1 6 November 19 1)

normal erythrocytes in a patient with lymphatic leukemia described a logarithmic curve compatible with the concept of a destructive factor acting at random at a constant rate The rate was so fast that loss from normal aging was obscured

Survival of normal transfused red cells in a patient with pernicious anemia was consistent with an active random de

mal and abnormal again because of the different appearance and cellular content of them The suggested combined technic is of value in studying cells of the lympho plasmo and megakaryocytic series and in the search for L E cells More accurate diagnosis is possible than with the Arinkin technic especially in lymphosarcoma plasma cell myeloma thrombocytopenic purpura leuko and pancytopenic states hypo and aplastic anemias and aleukemic leukemias

[As stated by this method both smears and sections of marrow particles may be examined thus diminishing the need for trephine biopsy —Ed]

Splenic Aspiration Clinical and Hematologic Considerations Based on Observations in 105 Cases Maurice Morrison A A Samwick Joshua Rubinstein Henry Morrison and Leo Loewe[3] (Jewish Hosp Brooklyn) analyzed results of splenic aspirations performed as adjunctive diagnostic procedures on 105 patients with various diseases

METHOD —The apparatus required are a 20 gauge needle dry syringe and alcohol sponge no anesthesia is necessary The patient is told to hold his breath Standing on the patient s left the operator needles the spleen clo e to the costal margin at the midclavicular line aspirates rapidly and promptly withdraws syringe and needle If necessary the procedure may be repeated immediately Total time varies from 5 to 10 seconds

Other diagnostic procedures included peripheral blood and bone marrow studies lymph node aspiration and biop y when possible pathologic study of the spleen after splenectomy and autopsy Correct diagnosis was made by blood study alone in 29 patients (27 6%) by combined bone marrow and blood study in 32 (30 5%) and by a combination of splenic aspiration and bone marrow and peripheral blood studies in 102 (97 2%)

The procedure is innocuous when limited to spleens large enough to permit the abdominal approach It should not be done on patients with bleeding tendencies The authors experience suggests that splenic aspiration facilitates identification of certain diseases previously difficult to diagnose before operation or autopsy osteosclerotic anemia extramedullary hemopoiesis Gaucher s disease (especially if absent in bone marrow) and spent polycythemia Since splenectomy is contraindicated if the spleen shows hemopoiesis [and the marrow does not —Ed] aspiration may be performed preoperatively

(3) J A M A 146 1575 1580 A g 25 1951

them The bloody fluid from the concave slide is placed in a Wintrobe hematocrit tube and centrifuged at 2 000 rpm for 10 minutes The fluid separates into a bottom layer of red cells a pinkish gray layer of marrow cells and particles a wide layer of plasma a top layer of fat and sometimes a layer of marrow particles below the fat The fat and plasma layers are discarded and smears made from the marrow layer Marrow particles may also be put on lens paper tied in a bag fixed in Zenker s solution and sectioned Control peripheral blood smears are also made

The technic for iliac crest spinous process tibial and rib puncture is essentially the same as that for sternal tap In the iliac crest the needle is pointed on top of the crest and the bone pierced down



Fig 49 (left) —Apl t ma w afte trog n mustard th apy d ed f om × 210 P n ytop
Fg 50 (ght) —Hyperpl t c m ow ed ced f om × 280 G ad 3 4 in ased cellul rity
(Co rtesy f P opp S Blood 6 585 599 J ly 1951)

and slightly out in its center Any large spinous process is suitable and is pierced straight through its center preferably with the patient sitting or prone Since the cavity is deep a 2 cm needle is used If a rib is easily palpable it may be punctured but usually only to diagnose malignancy and not as a routine procedure Rib margins are held between thumb and finger and a 1 1 5 cm. needle directed into the center For the tibia the lateral margins are held as before and a 2 cm needle directed midway between the fingers and slightly down The bone may be hard and considerable pressure may be necessary to penetrate the cavity

Presence of sodium heparin in the aspirating syringe allows complete use of any material obtained Interpretation includes study of peripheral blood direct particle and concentrated smears and the pattern of the entire material Diagnosis is based largely on the pure marrow smear Cellularity depends on the relative content of marrow and fat cells sinusoids and reticulum in this smear (Figs 49 and 50) Many smears should be studied because there may be considerable variation

In changing from the direct smear technic to that of marrow particle smears one must become familiar with the nor

results were in general normal Plasma cells were increased (2% or more) in 13 and in a few of these erythroid activity was depressed Degree of anemia and marrow changes were not however correlated except in the hemolytic cases

The L E cell was found in peripheral blood of 24 of 25 patients and in bone marrow of 18 of 20 patients—in the other 2 the cells were found in the peripheral blood There were no false positive results In one instance not suspected clinically the disease was found

Twenty two patients had palpable spleens but the enlargement varied greatly and showed little correlation with other hematologic findings At least half the patients had some enlargement of lymph nodes in 2 sufficient to suggest the diagnosis of lymphoma which was excluded

There was no consistent pattern of response in any of the formed blood elements in 12 patients given cortisone and/or ACTH whereas clinical changes were dramatic Lymphopenia was not seen as a new development All patients with the L E phenomenon before treatment retained it after treatment Response to transfusions was usually adequate but there was a tendency to form hemagglutinins Direct antiglobulin test results were positive in about 25% of the most recent series of patients Transfusion reactions also seemed more frequent but occurred at times when evidence of isoimmunization could not be demonstrated Conversely positive antiglobulin test results did not indicate an association between transfusions and the reactions

The most constant feature noted was anemia but a few patients showed no abnormality whatever The authors suggest that the L E cell be sought whenever there are unexplained fever leukopenia thrombocytopenia hemolytic anemia arthritis nephrotic syndrome or uremia of obscure etiology

L E Cell and Its Significance are discussed by Peter A J Smith[5] (Univ of Minnesota) In 1946 and 1947 Hargraves and Morton respectively studied biopsy specimens of heparinized sternal marrow from lupus erythematosus patients and described large round homogeneous purplish masses in the cytoplasm of polymorphonuclear leukocytes and extracellular masses of similar material surrounded by normal poly

(5) B t J D rm t 64 10 25 J y 195

as a precautionary measure Hemolytic icterus, Cooley's anemia sickle cell anemia and other hemolytic anemias did not present significant splenic hemopoiesis

[This like any new procedure will require experience before the findings can be interpreted to the best advantage Any blind puncture of an abdominal mass (e g., liver) does presumably carry a small risk which must be weighed against other possible ways of reaching a diagnosis —Ed]

Hematologic Aspects of Disseminated (Systemic) Lupus Erythematosus in 25 patients recently studied with cortisone and ACTH and 86 seen previously are presented by Sidney R Michael I Lutfi Vural Frank A Bassen, Louis Schaefer Mildred Bergman Lois Landin and Helen Michael[4] (Mount Sinai Hosp New York City) Diagnoses were based on characteristic clinical picture autopsy or biopsy findings Hematologic studies were made with accepted technics and the L E cell was detected by the Hargraves method

Of the 111 patients in both series 87 were anemic (under 12 Gm) on hospitalization and 24 were not although 15 of them were found anemic on subsequent test Anemia was usually normocytic and normochromic of moderate degree and seemed to depend on duration and severity of illness Hemolytic anemia was found in three patients in two the process was noted before transfusion the third had had transfusion two weeks before hospitalization Relationship between hemolytic anemia and the transfusions seemed unlikely the authors suggest that the differential diagnosis should include disseminated lupus erythematosus [Such cases have been reported —Ed]

Leukopenia (less than 5 000 white cells) on hospitalization was found in 47 leukocytosis in 10 and normal white cell counts in 54 Leukopenia developed in 19 others later Final counts in 25 patients showed leukocytosis usually with pyogenic complications or spread of underlying disease although only 1 patient had severe external bleeding 43 patients had thrombocytopenia (150 000 platelets or less) A few had hemorrhagic type rash Severe thrombocytopenia was apparently the initial manifestation of the disease in two patients One died seven another two years after splenectomy

In 32 cases bone marrow examination with differential counts showed only 1 with hypoplastic marrow in the others

(4) Blood 6 1059 1072 November 1951

and light absorption studies have indicated that the L E body consists of nuclear material of composition similar to that of the hematoxylin staining bodies described originally by Gross (1932) in postmortem preparations from patients with acute disseminated lupus erythematosus

The serum factor is a heat labile gamma globulin not normally present in human serums and antigenically quite distinct from any fractions in normal gamma globulin It may be destroyed by bacterial contamination but is not inactivated by storage for six months or by addition of cortisone In acute lupus erythematosus cerebrospinal fluid can induce the phenomenon Serum from patients with other diseases characterized by hyperglobulinemia does not produce the L E cell Absence of L E cells from the tissues—direct films of blood and marrow and autopsy histologic preparations—is a matter for speculation The consensus is that L E cells cannot be demonstrated in chronic lupus erythematosus without systemic manifestations The more ill the patient the more obvious the phenomenon after ACTH or cortisone therapy it may disappear temporarily Reports of this cell in other illnesses are extremely rare and are unconfirmed Although particular attention has been paid to the so called collagen diseases this cell has not been found in other members of that group

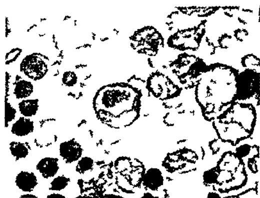
There are four methods of demonstrating the L E phenomenon (1) heparinized bone marrow (2) peripheral blood with or without an anticoagulant (3) plasma added to normal human or dog marrow and (4) scrapings from cantharides blisters Smith prefers the third Not only does it avoid the trauma of marrow biopsy in a patient who may be quite ill but it is more likely to show the L E phenomenon Any marrow except that from patients with leukemia pernicious anemia or infective conditions can be satisfactorily substituted

[This careful and extensive review deserves study in the original —Ed]

Simple Office Procedure for Demonstrating Lupus Erythematosus Cells in Peripheral Blood Hazel B Mathis[6] (New York Univ) demonstrated L E cells in large numbers in venous blood in each of 9 patients with clinical acute dis

(6) Blood 6 470 473 May 1951

morphonuclear cells Although most of the intracellular bodies were homogeneous a few showed a reticular pattern suggesting nuclear structure These leukocytes with the in clusions were called L E cells (Fig 51) and are to be dis tinguished from the so called tart cells The latter are histio cytes with a secondary nucleus in which the chromatin parachromatin and nuclear membrane can be detected They may be found in heparinized marrow from patients with any serious disease Others found L E cells in films made from the buffy coat of oxalated venous blood and L E cells have



F g 51 —H mogeneou L E body n yo ng polym pho ucl a c ll ed d f om X 675 (Cou t sy of Sm th P A J B t J D mat 64 10 25 Jan ary 195)

been produced by adding plasma from known cases *to* heparinized normal marrow Use of an anticoagulant is not necessary in any method utilizing peripheral blood Poly morphonuclear leukocytes resembling L E cells have been demonstrated in scrapings from the floor of blisters made by application of cantharides cerate to the skin of patients with *systemic lupus erythematosus and in several* cases this method has given positive results when marrow examinations have been negative

Although most L E *bodies* are *in polymorphonuclear cells* they are sometimes seen in eosinophils and histiocytes and may originate from the nuclei of lymphocytes if the buffy coat from a patient with lymphatic leukemia is ad mixed with L E serum and normal buffy coat Histochemical

of the tube with a wire loop are placed on a slide and emulsified with a drop of diluent and a film is made as previously described All preparations are air dried and stained Any Romanowsky stain may be used but the author prefers tetrachrome (MacNeal) stain which is applied for 1/2 minutes and an equal volume of distilled water added for 2 more minutes Slides are washed under running water drained dry and examined Figure 52 shows typical I E cells in such a preparation

Drug Induced Blood Disease is reviewed by J N Marshall Chalmers[7] (St George s Med School) Many drugs may reduce granulocytes in the blood but leukopenia and neutropenia do not necessarily indicate impending agranulocytosis further a normal leukocyte count can be obtained and agranulocytosis subsequently develop rapidly This suggests some peripheral destruction or loss of granulocytes in addition to the action on the marrow In many patients receiving thiouracil or a sulfonamide and developing neutropenia continuation of the drug has not caused clinical side effects the neutropenia remaining or correcting itself despite further dosage Agranulocytosis may occur any time during and sometimes after a course of treatment Even a small amount to a sensitized patient may precipitate it Laboratory tests give no dependable assistance in detecting onset or sensitivity

The possibility of agranulocytosis should be borne in mind when prescribing sulfonamide derivatives thiourea and its derivatives aminopyrine (pyramidon®) organic arsenicals (parenteral and oral) gold salts antihistamines diparcol tridione® mesantoin® and physical agents such as x rays radium and radioactive isotopes Barbiturates bismuth organic mercurials antipyrine and phenacetin® have among other drugs been reported on occasion as the probable cause of agranulocytosis Patients taking a drug known to be a potential cause of agranulocytosis should be instructed to stop treatment and consult their doctor immediately in case of sore throat fever or any illness This is the only real safeguard Penicillin is the most important treatment Other antibiotics may also be used as necessary Pentose nucleotide is still in use though some doubt its value If organic arsenic gold or mercury is the cause dimercaprol (BAL) should be given by injection together with the usual intensive penicillin therapy

(7) P t t 168 235 242 M h 1952

seminated lupus erythematosus but found none in 18 controls (multiple myeloma periarteritis nodosa, dermatomyositis discoid lupus rheumatoid arthritis rheumatic heart disease pernicious anemia miliary tuberculosis and five undiagnosed conditions)

TECHNIC —Venous blood 5 cc is placed in a sterile centrifuge tube with 3 drops of liquid heparin The tube is gently shaken and allowed to stand upright at room temperature until the cells have settled (usually about 30 minutes) The supernatant plasma and

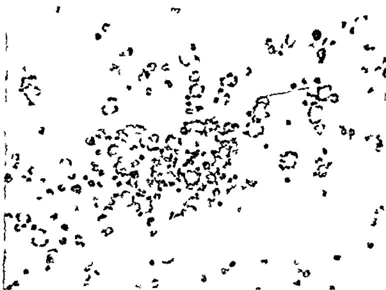


Fig 5 —Platelet mass preparation of peripheral blood of patient with acute disseminated lupus erythematosus many L.E. cells clumped about platelets from × 460 (Co te y f M th H B Blood 6 470 473 May 1951)

uppermost level of cells are transferred with a long stemmed pipet to a second sterile centrifuge tube This is incubated at 37 5 C for 45 minutes or allowed to stand at room temperature for 2 hours The incubated plasma is then centrifuged at 1 500 2 000 rpm for three minutes as excess centrifugation might pack the sediment too tightly Only 0 5 cc of the supernatant plasma is retained for subsequent use as a diluent

One drop of sediment is put on a glass slide which is kept in 95% alcohol and wiped dry just before using A second slide is placed on top and gently pressed until the sediment is spread thin the slides are then drawn apart in opposite parallel directions Small cartilage like masses of packed platelets taken from t ides

A number of drugs can cause methemoglobinemia and sulfhemoglobinemia (enterogenous cyanosis) Sometimes the conditions coexist Clinically there is no evidence of heart or lung disease to account for the cyanosis and the patients are not breathless A slight or moderate hypochromia often exists and occasionally associated hemolytic anemia has been de scribed Spectroscopic examination of the blood is required to demonstrate the abnormal hemoglobins Sulfonamides may give rise to either type of altered hemoglobin Phenacetin acetanilid trional ® sulfonal ® pamaquin pyridium® and potas sium chlorate have also been reported as causes of one or both types Avoidance of sulfur containing saline purgatives in those receiving sulfonamide therapy has been said to re duce incidence Methemoglobinemia may be actively treated by reducing agents such as ascorbic acid and methylene blue intravenously or orally The effect is temporary if the causal drug is continued Prohibiting the drug causes methemo globinemia to disappear in a few days Sulfhemoglobin cy anosis may persist for a longer time Not to be confused are rare cases of congenital or idiopathic enterogenous cyanosis

Sulfonal ® trional ® barbiturates sulfonamides and organic arsenicals may give rise to porphyrinuria Analysis of the urine by a biochemist familiar with identification of por phyrins is advised rough tests are unreliable Drug induced porphyria of clinical gravity is rare patients show ing this phenomenon may have a latent inborn error of metabolism brought to light by the drug

[Having in m nd their toxic possib l ties may prevent unnecessary or excessive use of such drugs by physicians in the absence of clear indications for the administration —Ed]

***Successful Transfusion of Previously Frozen Human Red* Cells** is reported by P L Mollison and H A Sloviter[8] (London)

METHOD —ANRh positive blood was used for freezing and OMRh positive blood served as the control After the blood had been stored several days supernatant plasma was withdrawn from each bottle for resuspension of the recovered cells To a diluent of 30 Gm glycerol and 0 85 Gm NaCl/100 cc of solution in a Pyrex bottle was added an equal volume of concentrated red cell suspen sion the mixture was kept at 4 C for one hour It was then frozen while rotating in a —79 C bath (solid CO alcohol) and kept at that temperature two to three hours It was next thawed in a water

(8) L t 2 86 864 Nov 10 1951

Drugs to remember as possible causes of thrombocytopenia and purpura are sedormid* organic arsenicals sulfonamides gold salts and physical agents (x rays radium and radioactive isotopes) The most valuable line of treatment after stopping the drug lies in repeated transfusion preferably of fresh blood Repeated transfusions over weeks may be necessary before there are signs of recovery Provided death does not occur from hemorrhage or infection platelets return in most cases and recovery ensues Local treatment for hemorrhage may be with thrombin, fibrin foam or viper venom Antibiotics should be used to prevent infection Splenectomy has no place in the treatment of these acute purpuras For arsenical and gold thrombocytopenic states BAL should also be given Nonthrombocytopenic allergic or toxic purpuras have been observed following many drugs including belladonna epanutin, quinine quinidine copaiba salicylates ergot and phenobarbital Treatment after discontinuation of the drug is symptomatic since this form of allergic purpura is rarely serious

As causes of aplastic anemia again organic arsenical organic gold and sulfonamides head the list Mesantoin* tridione* folic acid antagonists nitrogen mustards atabrine* bismuth thorotrast* colchicine chloramphenicol x rays and radioactive substances are among the agents which probably have given rise to marrow aplasia or hypoplasia The drug should be stopped and repeated blood transfusions of concentrated cells given with full appreciation of the hemodynamics of these severe anemias Transfusion must be done slowly to avoid cardiac failure Since these patients may require enormous quantities of blood correct rhesus grouping is necessary, even then other uncommon antibodies may develop Although the outlook is always grave blood transfusion is worth continuing since recovery is possible in a small proportion of cases

Hemolytic anemias may follow use of sulfonamides organic arsenicals phenothiazine phenylhydrazine phenylsemicarbazide antihistamines mephenesin pamaquin (particularly in association with atabrine* or quinine) and quinine itself [In some the mechanism is injury of red cells by oxidant derivatives of the drugs as with naphthalene See section on hemolytic anemia this YEAR BOOK —Ed]

because of shielding by intervening objects Laboratory experiments have shown that all shielding tends to increase resistance to radiation and to modify the response of hemopoietic organs [See following article —Ed] No circulating blood cells except lymphocyte are injured by amounts of radiation in the lethal range All evidence points to destruction of stem cells (blasts) as being responsible for the peripheral blood changes which follow normal attrition after cessation of production by the hemopoietic organs Injury to the blast cells may result in their complete or partial destruction or in interference with their maturation

Erythroblasts are equal in sensitivity to any of the other blast cells After exposure to lethal amounts of radiation there is a minimal decrease of 1% of red blood cells daily (in addition to erythrocytes lost by their increased destruction by hemorrhagic tendency or from injury) until regeneration occurs Since the life span of the granulocyte is estimated at one to four days [or less —Ed] with no production their disappearance will be rapid The degree of depression in the lymphocyte count is a function of the amount of radiation up to low lethal doses when response becomes maximal With doses below lethal range the lymphocytes tend to recover rapidly with higher doses there is no or slight tendency for them to reappear in the peripheral blood Radiation above LD_{100} in dogs causes the platelet count to increase slightly in the first 3 4 days then to disappear linearly for about 6 days approaching zero about 9 10 days after exposure Megakaryocytes are present in the bone marrow in significant numbers for the first three or four days With the decrease in platelet count there is a well correlated increase in whole blood clotting time This increase i not proof that thrombocytopenia is the cause of decreased coagulability With lower radiation levels there are minimal changes in the platelet count

The hemorrhagic manifestation of acute radiation injury usually is a florid purpura but hematomas epistaxis or gastrointestinal and urinary tract bleeding without diffuse purpura are also seen Predisposing factors to hemorrhage are pronounced thrombocytopenia ulcerations into the blood vessels from ulcers in the oral and gastrointestinal tract mucosa increased capillary fragility and inconstant clotting defect

bath at 37 C and then dialyzed in seamless cellulose sausage casing against a 6% glycerol saline solution at 4 C The red cells were separated by centrifugation washed with saline and suspended in the plasma previously set aside for this purpose

In all operations sterile equipment and aseptic technic were used Samples of all mixtures and products were taken for culture and red cell suspensions were not transfused until five day aerobic and anaerobic cultures proved negative Thus the red cells were transfused 7 days after freezing and 11 days after being drawn Final yields of red cells after freezing were about 70% the original number Bacterial contamination occurred in only 1 of 15 batches Control bloods not opened until the day of transfusion were also stored at 4 C

When a trial transfusion with 100 cc had no unfavorable effects three recipients with iron deficiency anemia and AMRh positive blood were given both control and previously frozen red cells Concentration of surviving cells of both was estimated by differential agglutination

No untoward effect followed full transfusion When survival of frozen and unfrozen red cells was compared in the same recipient that of the frozen red cells was better in one instance a little worse in another and indistinguishable from the control in a third Although frozen cells had been stored for 11 days in addition to the short period at —79 C an average of 90% of the number transfused was present in the recipient s circulation the day after transfusion (control 86%) and 40% 60 days later (control 43%)

At ordinary storage temperature (5 C) red cell deterioration results mainly from continued metabolic activity At —79 C there can be no significant metabolic activity Hitherto hemolysis has been the main problem in using low temperatures This method opens the way to possible long storage of red cells [and hence the elimination of the loss of the huge amounts of red cells now discarded in the form of over age conventional bank blood or red cells separated in the preparation of plasma and its fractions —Ed]

Hematology, Diagnosis and Therapy of Radiation Injury are discussed by Eugene P Cronkite[9] (Naval Med School Bethesda Md) Practically speaking the entire body will rarely be exposed to ionizing radiation after atomic explosion

(9) U S Arm d Fo c s M B ll 2 1019 1026 J ly 1951

the count exceeds 1 500 Careful attention to personal hy giene and meticulous aseptic technic in giving hypodermic in jections will help prevent infection Treatment of the hemor rhagic phase is currently unsatisfactory Rutin vitamin P fac tors and various flavonones have not yet proved valuable in radiation injury nor have other measures been effective under laboratory conditions Anemia may be combated by ample whole blood or washed red blood cell transfusions A mini mum of about 5 units of blood is required for each radiation casualty during the first month after exposure Management of disturbances in acid base and electrolyte equilibrium fol lows standard procedure

[This article contains an excellent summary of present knowledge The next article concerns experimental evidence for a protective effect of unirradiated splenic tissue a finding that may lead to important practical applications —Ed]

Further Studies on Recovery from Radiation Injury are reported by L O Jacobson E L Simmons E K Marks E O Gaston M J Robson and J H Eldredge[1] (Chicago) An earlier report indicated that the LD_{50} of whole body x radiation for intact young adult mice is approximately 550 r and that only rarely would a mouse survive more than 800 r whereas 40% survive 1 025 r if the spleen is mobilized and lead shielded during exposure Also in contrast to no shield ing no anemia and only temporary leukopenia and thrombo cytopenia appeared after 1 025 r with spleen shielded

Because the reticuloendothelial tissue of the shielded spleen or appendix might provide many free hemopoietic cells for blood stream transport to the destroyed hemopoietic tis sue experiments were designed to minimize likelihood of such transport or colonization After 1 025 r whole body x radia tion without spleen shielding four fresh spleens from mice 1 7 days old were placed unanchored in the peritoneal cavity of each irradiated mouse 50% outlived the 28 day observa tion period During the first few days only leaking of tissue juice from implants occurred Free cells became necrotic and histologic reconstitution did not take place for six days or more Recognizable takes were seen in 75% of animals surviving 30 days In the other 25% either juice from spleen implants was enough to initiate recovery or temporary takes occurred Since beginning recovery of marrow and lymphatic

(1) J Lab & Clin. Med 37 683 697 M y 1951

sometimes ascribable to an anticoagulant of undetermined na ture

The following hematologic observations help in determin ing the prognosis of radiation illness The absolute lympho cyte count is a good index of relative exposure to sublethal radiation Reticulocytosis is usually followed by recovery Death generally occurs if the granulocyte count falls below 1 000/cu mm if platelets disappear or if clotting time is pro longed with concomitant purpura Survival usually follows if the granulocyte count remains 1 500/cu mm

After an atomic bomb explosion high in the air radiation injury will vary from sub to supralethal and will be combined with thermal and traumatic injuries Evaluation of symptoms is the simplest approach to diagnosis of the relative degree of radiation injury For this purpose radiation casualties may be divided into three groups In group 1 (supralethal radia tion survival improbable) vomiting will occur in a few hours followed by prostration diarrhea anorexia fever and early death There will be profound depression of the leuko cyte count within 48 hours Mortality will be almost 100% In group 2 (lethal radiation survival possible) vomiting will subside in a few hours There will be an asymptomatic period of one to three weeks followed by a recrudescence of illness with purpura epilation oral and cutaneous lesions wound in fection and bloody diarrhea Mortality will be about 50% without treatment In group 3 (sublethal radiation survival probable) there will be no vomiting on the day of bombing Late symptoms if any will resemble those of group 2 Radia tion injury in this group can usually be detected only by serial leukocyte studies Mortality will be practically nil if there are no complicating burns or trauma

Currently nothing can be done to improve survival rates after exposure to supralethal radiation Persons who survive exposure to lethal and sublethal radiation constitute a problem for long term study for possible latent effects (cataracts leu kemia cancer and possible genetic effects of radiation in off spring) The lethal factors in group 2 are infection hemor rhage anemia and disturbance in acid base and electrolyte equilibrium For prophylaxis antibiotics should be given orally about 7 10 days after exposure or when the leukocyte count is below 1 500/cu mm and should be con until

pearance of the white pulp Megakaryocytes appeared in four to five days granulocytopoiesis about the sixth day and by the eighth lymphatic tissue reappeared coincident with bone marrow recovery and erythroblast reduction in the spleen

The evidence appears to favor the assumption that shielded tissues produce a type of noncellular substance which benefits recovery of irradiated animals However the possibility that irradiation produces a toxin which shielded or implanted tissues somehow detoxify has not been eliminated That irradiated tissue can be stimulated by postirradiation therapy to recovery earlier than previously supposed is encouraging

[Recently spleen homogenates (presumably containing viable cells) have been shown to exert protection on intraperitoneal injection Ultrasonic vibrations destroy this property —Ed]

Results of Splenectomy in Banti's Syndrome According to Robert H Durham (Henry Ford Hosp) the current concept of this syndrome is that of an obstructive lesion of the splenic or portal vein or the intrahepatic venous system with *resulting portal hypertension and congestive splenomegaly* Laennec s cirrhosis is present in about 70% of cases although with an extrahepatic obstructive lesion the liver is usually not involved An intrahepatic obstruction may exist though the liver appears grossly normal During development of splenomegaly evidence of hypersplenism may be found in the blood and bone marrow Since the portal system has no valves collateral circulatory changes develop being most pronounced when the lesion is in the liver or portal vein Pathologically the spleen shows gradually developing congestion with atrophy of the reticulum and fibrous tissue replacement

Splenectomy has long been considered the logical treatment If only the splenic vein is obstructed the operation should decrease venous pressure so that collateral circulation would be unnecessary If the obstruction is in the portal vein or liver splenectomy should greatly reduce portal pressure since about 40% of the blood going through the portal vein comes from the splenic artery Some observers believe that splenectomy has no deleterious effect on an existing cirrhosis and others believe that reduction in venous pressure permits better response of the liver to supportive therapy However most statistics indicate that in severe cirrhosis with pro

(2) A n I t Med 34 137 1381 J 1951

tissue was evident in four days in some animals tissue juice factors appear to be related at least at this dosage level

Initially adult spleen implants were ineffective in enhancing survival It was later found however that incising of the adult spleen capsule before implantation enabled some 50% of mice to survive 1 025 r if a single such spleen was implanted immediately after irradiation

When volumes of mouse livers equal to 8 times mouse spleen were shielded during exposure hemopoietic recovery was hastened as compared with animals exposed without shield but recovery was not as speedy as after spleen shielding This further suggests that the factor responsible is probably humoral Lead shielding of the intestine also enhanced survival All tissues which produce this phenomenon when

SURVIVAL OF MICE EXPOSED TO 1 025 R WITH LEAD SHIELDING OF SURGICALLY EXTERIORIZED SPLEEN WITH REMOVAL OF SPLEEN AT VARYING INTERVALS AFTER X RAY

Time of Splenectomy after X ray	No of Mice	Survival %	Dosage in r
1 hr	41	73 4	1025
6 hr	13	46 2	1025
12 hr	66	39	1025
1 day	27	85	1025
2 days	40	55	1025

shielded have reticuloendothelial constituents as their common feature

Glutathione or cysteine given immediately before irradiation reduced O_2 tension and cyanide intoxication *during* irradiation will reportedly reduce mortality These are beneficial prophylactic measures that are ineffective if taken after exposure To determine how long the lead shielded spleen must remain intact after irradiation for maximal effect spleens of exposed mice were removed at various intervals after irradiation Results (see table) suggest that leaving the spleen intact for 1 6 hours is as effective as 48 hours In a preliminary study two days after irradiation four baby spleens were implanted into the peritoneal cavity of 24 mice 5 lived 23 days and 4 over 28 days indicating that late addition of the factor is at least partly effective

Bone marrow of mice irradiated with shielded spleens was destroyed but spleens showed intense ectopic blood formation mainly erythroblastic at three days and decided disap-

myeloid erythroid ratio is a *further* contraindication Splenectomy should not be performed on children whose blood picture is not entirely typical or on severely anemic patients Operative mortality is decidedly higher in patients over 40

[Recurrent hematemesis from varices is the primary indication for surgery in this syndrome In addition to splenectomy the development of anastomatic vascular surgery by Blakemore and Whipple provides another means of lowering portal hypertension whether the obstruction is intrahepatic or involves the main portal vein trunk

Splenorenal and portacaval anastomoses are the chief procedures that have been employed They should always be contemplated at the time of the original splenectomy Despite authoritative statements the exact nature of the anemia of Banti s syndrome is obscure Decrease of platelets and prothrombin or its accelerators enhances the tendency to bleeding in these patients —Ed]

HEMOLYTIC ANEMIAS

Significance of Hemoglobinemia and Associated Hemosiderinuria, with *Particular Reference to Various Types of* Hemolytic Anemia Hemoglobinemia is the existence of extracorpuscular hemoglobin in excess of 5 mg /100 ml When concentration of plasma hemoglobin exceeds the renal threshold (90 100 mg /100 ml) *hemoglobin is excreted* in the urine Gross hemoglobinuria has called attention to certain rare blood dyscrasias such as paroxysmal hemoglobinuria favism blackwater fever and transfusion reactions but it has also been reported in more common conditions i e acquired hemolytic anemia Mediterranean anemia and sickle cell disease

Hemoglobinuria is always secondary to hemoglobinemia and frequently directs attention to it Degrees of hemoglobinemia too small to cause hemoglobinuria have seldom been identified nevertheless they exist When plasma hemoglobin is 10-40 mg /100 ml the plasma may lack the suggestive reddish tint not only because hemoglobin concentration is slight but because of presence of other pigments e g orange bilirubin and brown methemalbumin which give plasma a tan hue

William H Crosby and William Dameshek[3] (Boston) studied plasma hemoglobin *concentration* and examined urine for presence of hemosiderin (iron staining pigment) in pa

(3) J Lab & Cl Med. 38 829 841 December 1951

nounced collateral circulation and ascites the operation is of little or no value

The incidence of hemorrhage in these patients has been estimated to decrease from 33 to 50 per cent after splenectomy Theoretically, the reduction should parallel the 40 per cent reduction in blood from the splenic artery, plus the effect of correcting thrombocytopenia Occurrence of hematemesis during the first two postoperative weeks usually indicates extension of the thrombotic process in previously unobstructed branches of the portal vein

A hypersplenic effect may occur early in Banti s syndrome with maturation arre t of ervthroid elements in the bone marrow myeloid hyperplasia and moderate peripheral anemia and leukopenia As splenomegaly increases there is maturation arrest of myeloid and megakaryocytic tissue With advanced cirrhosis of the liver the marrow shows pronounced erythroid immaturity and changes in myeloid tissue Although the characteristic thrombocytopenia is immediately corrected by splenectomy overcompensation often develops greatly increasing the postoperative thrombotic hazard Consequently patients with preoperative thrombocvtosis are poor risks Splenectomy relieves the hypersplenic effect on the peripheral blood and generally eliminates secondary anemia leukopenia and thrombopenia Except in a few cases in which the splenic vein alone is involved splenectomy does not correct the disease process but does modify its course by improving bone marrow function and decreasing hemorrhage

Durham reviewed the records of 70 patients Of 31 who underwent splenectomy 6 died of hemorrhage or thrombosis and embolism before the fourteenth postoperative day 15 died later of hemorrhage and other causes and 5 were alive 1½ 10 years after operation Two other survivors underwent splenectomy 22 and 23 years ago neither had postoperative hemorrhage and both are well

Careful selection of patients may improve results of splenectomy in Banti s syndrome The operation is rarely justified in progressive decompensating liver disease or in the presence of preoperative thrombocytosis Results are invariably poor when the bone marrow shows toxic depression rather than hyperplasia An erythroblastic marrow with reversal of the

without increasing plasma hemoglobin survived to be hemolyzed intravascularly without consequent hemoglobinemia

Hemosiderinuria was invariably found when hemoglobinemia was present. Amount of hemosiderin varied with concentration of plasma hemoglobin usually but not invariably when plasma hemoglobin was about 50 mg/100 ml a large amount of urinary pigment was found and no hemosiderin was found in urine of patients without hemoglobinemia although this has been reported by others in hemochromatosis and pernicious anemia

Diagnostically demonstration of hemoglobinemia is unequivocal evidence of abnormal hemolysis and therefore of hemolytic disease. Presence of hemoglobinemia may distinguish between sickle cell trait and sickle cell anemia between mild and severe Mediterranean anemia and between acquired hemolytic anemia and hereditary spherocytosis. In acquired hemolytic anemia continued hemoglobinemia is an unfavorable prognostic sign since it indicates a severe hemolytic process. It is the first sign to diminish with improvement

Antibody Titer in Maternal and Infant's Serum as Indication for Treatment in Hemolytic Disease of Newborn. Because there is no reliable clinical picture which allows estimation of severity of hemolytic disease of the newborn G A Kelsall and C H Vos[4] turned to laboratory tests. In 43 cases standardized antiglobulin tests for antibodies in mothers and infants blood were used to predict severity. Titration of maternal antibodies at delivery gives some indication of prognosis and treatment to be adopted (exchange transfusion simple transfusion no treatment). Severity of the disease can be even better determined by titration of antibodies in the infants cord blood. Subtraction of the infants serum titer from that of the mother gives a measure of the antibodies absorbed by the cells of the child and is referred to as the titer difference. Whether this absorption is upon the erythrocytes alone or upon the tissue cells in addition has still to be definitely proved

An early antepartum check of the mother for Rh status should be made. If she is Rh negative the father should be tested and then the siblings if necessary. Examinations for maternal antibodies should be made each month however

(4) M J A 1 1 349 356 M 15 1952

tients with acquired hemolytic anemia hereditary spherocytosis severe Mediterranean anemia and sickle cell anemia As controls observations were made on more than 100 normal plasmas and plasmas of over 100 patients without blood dyscrasias Blood was obtained by venipuncture without suction using a syringe lightly coated with mineral oil When the needle was removed, 5 ml blood was allowed to run gently down the side of a test tube containing 200 units of heparin Blood and heparin were mixed by gently rolling the tube between the palms of the hands One ml of blood was centrifuged for 10 minutes at 1 500 rpm and the plasma withdrawn and analyzed for hemoglobin using Ham s modification of Bing and Baker s method Urine was tested for hemosiderin using the Prussian blue reaction In none of the controls did plasma hemoglobin exceed 4 mg /100 ml

In 10 patients with acquired hemolytic anemia examined during severe bouts of hemolysis plasma hemoglobin was always elevated (10 50 mg./100 cc in one patient 166 mg) As crises subsided hemoglobinemia diminished and often disappeared In several patients ACTH produced a well defined partial or complete remission and abnormal plasma hemoglobin regressed during therapy There was no variation in degree of hemoglobinemia before and after sleep

In 13 patients with hereditary spherocytosis (congenital hemolytic jaundice) plasma hemoglobin was always low usually below 3 mg./100 ml In the few cases in which hemoglobinuria has been reported with hereditary spherocytosis the crisis may well have been due to acquired hemolytic disease superimposed on the hereditary Hemosiderinuria was absent in all these patients

In 3 patients with severe Mediterranean anemia and 2 with sickle cell anemia hemoglobinemia was consistently found with plasma hemoglobin usually between 20 and 25 mg /100 ml Splenectomy was done in one patient with moderately severe Mediterranean anemia who had for many years required occasional and later frequent transfusions Plasma hemoglobin was always below 3 mg./100 ml After operation clinical improvement was remarkable and transfusion no longer necessary However plasma hemoglobin became and remained elevated to about 25 mg./100 cc. This suggests that red cells which previously had been destroyed in spleen

antibody titer difference may be a useful indirect measure [If confirmed this would seem a valuable advance —Ed]

Antenatal Prediction of Hemolytic Disease of the Newborn Preliminary survey of advantages of analyzing the liquor amnii at artificial rupture of the membranes indicates even greater value of specimens taken earlier in pregnancy D C A Bevis[5] (Manchester) obtained amniotic fluid by abdominal paracente is starting at the 28th week and repeated this at fortnightly intervals until delivery He infiltrated a point midway between umbilicus and symphysis pubis with 1% procaine carefully avoiding large skin vessels Uterine paracentesis was then performed by spinal needle and approximately 3 ml liquor amnii was aspirated The puncture was then sealed with plastic

From 69 patients 158 specimens of liquor amnii were examined Of the patients 54 were sensitized Rh negative women 30 of whom gave birth to infants with hemolytic disease of the newborn Despite repeated paracentesis no ill effects were noted in the mothers apart from slight abdominal discomfort No instance of premature labor or stillbirth could be ascribed to the procedure and there was no evidence of skin trauma in the infants Specimens were extensively investigated chemically but only the nonhematin iron and the urobilinogen concentrations proved of prognostic value The hemolytic process produced notable changes in these concentrations Iron concentration in the liquor amnii was relatively constant throughout the study When the highest value in each case was taken and its logarithm plotted against fairly well fitted cord blood hemoglobin points the inverse relationship of these values was evident Estimation of iron thus appears most valuable in assessing prognosis for the fetus Although urobilinogen concentration does not behave in the same way fetal disease always accompanied sudden though often transitory decrease in the concentration This decrease does not clearly indicate the degree of the hemolytic process but a large decrease is of grave significance

[The wide scatter of the values shown in the author s charts does not appear to lend itself to practical interpretation Why a hemolytic proce s should result in either abnormally high or low values of nonhematin iron or urobilinogen is not clear —Ed]

(5) L ncet 1 395 398 Feb 23 1952

if antibodies are present once a week after the 32d week If the titer is above 64 and rising, pregnancy should be terminated at the 36th week This is also advised if the father is homozygous and the maternal titer high and stationary Only if the father is heterozygous and the titer stationary at a low level do the authors believe in watching the titer weekly as pregnancy continues for infants of heterozygous fathers may be Rh negative In this series a dangerously high maternal titer was found only when the father was homozygous

In six cases Rh negative women mated to heterozygous men had Rh negative infants In each there were residual antibodies from previous pregnancies with immunization in each level of antibodies was the same in the mother s and infant s blood In 10 mild cases of hemolytic disease of the newborn (Rh positive infants from Rh negative mothers) the highest maternal titer was 64 and the highest infant s titer was 8 Simple blood transfusions sufficed to tide over these children

There were 20 severe cases of hemolytic disease The maternal antibody titer was 64 2 048 the titer of infant s cord blood 16 512 Those children not g ven transfusions died One child given simple transfusions was mentally defective and died at 10 months One child survived who was given simple transfusions The rest received exchange transfusions one died at 38 hours with kernicterus Because of occurrence of tetany with transfusions of citrated blood the authors gave up this type of transfusion and now use heparinized blood No signs of cardiac overloading have been observed nor troublesome cyanosis salivation or irritability such as was noted when citrated blood was used Antibodies persist in the blood of the infants even though the cells have been exchanged It is important therefore to use blood which contains no antibodies blood obtained from males should be used if antibody tests cannot be carried out The antibodies can be reduced by exchange transfusion The blood required is three times the infant s blood volume (40 ml./lb body weight)

The authors believe that infants with hemolytic disease die not of anemia per se but rather as a result of the antigen antibody reaction effect on tissues of which the mother child

patient presents chronic hemolytic anemia with moderate jaundice hepato and splenomegaly chronic leg ulcerations recurrent bouts of fever with osteoarticular pains and crises of severe abdominal pain Although many patients attain adulthood the disease is serious and fatal

Hematologically microdrepanocytic disease differs from sickle cell anemia in several respects indicating simultaneous sicklemia and microcythemia Microdrepanocytic disease is characterized by hypochromic anemia sicklemia decreased red cell fragility microcytosis and marked abnormalities in erythrocyte morphology (anisocytosis poikilocytosis severe hypochromia and target cells as seen in Fig 54) In sickle cell anemia the anemia is normochromic and macrocytic and poikilocytosis is moderate and inconstant some target cells are also found (Fig 53) Characteristically patients with microdrepanocytic disease have the gene of both sicklemia and microcythemia the parents having transmitted one or the other of the two genes In 7 of 11 families studied one parent exhibited the sickle cell and the other the microcythemic (Mediterranean) trait in 1 family the father himself had microdrepanocytic disease and the mother was a microcythemia carrier In the other three families one parent showed sickle cell trait the other parent had died but microcythemia was found in some of his relatives or children

Genetic studies of these families suggest that microcythemia and sicklemia genes are located on different chromosomes and are inherited independently of each other

Pathogenesis of Sickle Cell Anemia A Review is presented by Karl Singer[7] (Michael Reese Hosp) In 1840 Gulliver discovered peculiar crescent shaped red cells in blood films from several exotic deer in the London Zoo In 1910 Herrick described the first clinical case of sickle cell anemia in man The disease is a hereditary syndrome confined almost exclusively to the Negro There are two principal forms (1) sickle cell trait or sicklemia without clinical symptoms and (2) sickle cell anemia About 8% of Negroes harbor the trait The proportion of patients with sickle cell anemia to the total number of sicklemic persons is estimated at 2 5 15%

Susceptible red cells change into sickle cells *only* if the contained hemoglobin is reduced as by exposure in vitro

(7) Am J Clin P h 21 858 865 Sept mbe 1951

Genetic Aspects of Sickle Cell Anemia and Microdrepanocytic Disease E Silvestroni and I Bianco[6] (Univ of Rome) studied families of healthy individuals with the drepanocythemia (sickle cell trait) and patients with sickle cell anemia all of them of Sicilian or Central and Southern Italian stock Study of two healthy families with the sickling trait indicated that in the White as well as the Negro it

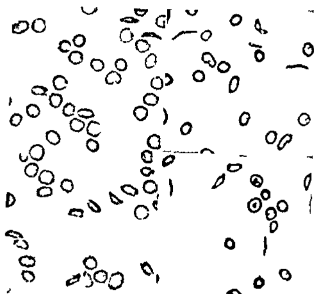


Fig 53 (left) —Photomicrograph of blood smear of sickle cell anemia showing slight degree of poikilocytosis and hypochromia
Fig 54 (right) —Blood smear of two patients with microdrepanocytic disease showing extreme degree of poikilocytosis hypochromia and numerous target cells (Courtesy of Silvestroni E and Bianco I Blood 7 429 435 April 1952)

behaves as a mendelian dominant transmitted in consecutive generations Asymptomatic individuals are heterozygous carriers and their offspring are either normal or carriers of the trait Both parents of all three patients with sickle cell anemia had the sickle cell trait

Microdrepanocytic disease was discovered in 22 of 63 individuals belonging to 9 of 11 families studied In this condition one parent of the patient has the sickle cell trait and the other has microcythemia (Mediterranean anemia) The

(6) Blood 7 429 435 April 1952

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(7) Am J Cl P th 21 858 865 S pt mb 1951

to gas mixtures containing little or no oxygen or to a reducing agent such as sodium metabisulfite The latter method conveniently deprives the hemoglobin of all its oxygen and sickling occurs to the same extent in both trait and 'anemia cells In vivo however in the venous circulation of patients with sickle cell anemia where oxygen content is reduced to about 14 vol % 30-60% of the red cells sickle whereas less than 1% sickling occurs in persons with the trait and no anemia

Sickle cell disease is characterized chiefly by (1) hemolytic anemia (2) leg ulcers (mostly in adults) and (3) periodic attacks of severe muscle and joint or abdominal pains called crises Though a disposition for vascular occlusion exists in this disorder the thrombotic theory of pathogenesis is an oversimplification

Studies of survival time show that trait cells act like normal ones in the circulation of patients with sickle cell anemia (surviving about 120 days) Sickle cell anemia cells exhibit a markedly shortened life span (15 60 days) probably due to the greater susceptibility of sickled cells to the mechanical stress to which they are subjected in the circulation The shortened red cell life span also explains the so called aplastic crisis in which inhibition of red cell formation in the course of an acute virus infection in a person with a hemolytic syndrome may produce a precipitous fall in the red cell count in a few days

Since sickling distortion occurs with only reduced hemoglobin it is probable that this pigment is somehow responsible for the phenomenon Sherman noted that sickle cells show definite birefringence under the polarizing microscope and Ponder found that after hemolysis the ghosts of red cells do not undergo sickling in low oxygen tensions In 1949 Pauling discovered that sickle cell hemoglobin differs electrophoretically from normal hemoglobin moving as a positive instead of negative ion Harris then showed that concentrated solutions of reduced sickle (S) hemoglobin had characteristic tactoid formation on examination with the phase microscope Tactoids are made of long thin rodlike particles with a parallel and equidistant arrangement and have a striking resemblance to sickle cells Harris concluded that a sickled red cell is essentially a hemoglobin tactoid thinly veiled and

somewhat distorted by the cell membrane [See the 1951 YEAR BOOK p 271 —Ed]

In the Tiselius apparatus trait cells show concentrations of 23 45% of pathologic pigment (S hemoglobin) Since with completely reduced hemoglobin all trait cells sickle these cells must contain a mixture of N (normal) and S hemoglobins Anemia cells were first thought to contain only S hemoglobin but some patients with sickle cell anemia have been shown to have 5 20% of electrophoretically normal hemoglobin

Recent studies in Singer s laboratory have demonstrated a third type of hemoglobin which is constantly found in the anemia but not in the trait cells This was identified as fetal (F) hemoglobin because of its resistance to denaturation by alkali in a 1 minute test exposure to alkali In the newborn 60 90% of the hemoglobin is of this type Since reduced F hemoglobin does not readily form tactoids only a few sickled cells (already with enough S pigment) are found in infants Production of the fetal compound may continue till the end of the second year in normal children In 90 carriers of the trait over age 2 F hemoglobin was always absent but in 45 with sickle cell anemia regardless of age an alkali resistant hemoglobin was consistently present (2 24% of the total pigment) Apparently trait cells contain N and S hemoglobin whereas anemia cells have S and F pigment

It is of interest that F hemoglobin is also found in other hereditary hemolytic syndromes In Cooley s anemia up to 34% is present and one of four families with hereditary spherocytosis showed a fetus like pigment Though no dis tinct relation has been observed between severity of anemia reticulocyte output and the varying quantity of F pigment in different patients preliminary studies indicate that alkali resistant hemoglobin may not be equally distributed in all erythrocytes and that cells containing F compound may sur vive longest

There is general agreement that sickle cell disease is hereditary It has been suggested that sickle cell anemia is the homozygous condition and that the trait will occur in heterozygous persons Singer observed two families in which blood of the mothers of children with severe sickle cell anemia did not show the sickling phenomenon even when the hemo

to gas mixtures containing little or no oxygen or to a reducing agent such as sodium metabisulfite The latter method conveniently deprives the hemoglobin of all its oxygen and sickling occurs to the same extent in both trait and anemia cells In vivo however in the venous circulation of patients with sickle cell anemia where oxygen content is reduced to about 14 vol % 30 60% of the red cells sickle whereas less than 1% sickling occurs in persons with the trait and no anemia

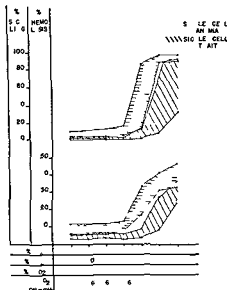
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susceptibility of cells to sickling at low oxygen tensions [That is as is well known a fall in pH reduces the per centage O saturation of hemoglobin at a given O tension Sickling is a function of the amount of reduced abnormal hemoglobin —Ed]

Analysis of results demonstrated that in general trait erythrocytes are more resistant to changes in both pH and



F g 55 —Eff t f y g on t t f yg n d t g w th 10 p t CO n m d tr t yth ocyt (Court y f La g R D t J L b & Cl M d 37 789 80 M y 1951)

oxygen tension than are anemia cells The authors suggest that this difference in susceptibility to sickling plus the ac companying differences in mechanical fragility may explain why sickle cell anemia and sickle cell trait differ in clinical and hematologic manifestations

New Inherited Abnormality of Hemoglobin and its Inter action with Sickle Cell Hemoglobin reported by Eugene Kaplan Wolf W Zuelzer and James V Neel[9] was found

(9) Blood 6 1 40 1259 Dec mbe 1951

globin was completely reduced by various procedures Such a finding is still compatible with genetic theory if the assumption is made that in some heterozygous persons the amount of S hemoglobin may be too small to permit tactoid formation and thus produce sickling Further studies of this problem are obviously needed

Effect of Oxygen Tension and of pH on Sickling and Mechanical Fragility of Erythrocytes from Patients with Sickle Cell Anemia and Sickle Cell Trait In atmospheres of carbon dioxide or in the presence of reducing agents nearly 100 per cent of both trait and anemia erythrocytes become sickled The capacity to sickle is possessed equally there fore by the two types of red cells yet their in vivo behavior is so different that a shortened survival time and hemolytic anemia are characteristic of sickle cell anemia whereas normal survival time and total red cell values are found in sickle cell trait

Robert D Lange Virginia Minnich and Carl V Moore[8] (Washington Univ) studied erythrocytes of both sickle cell anemia and trait patients When blood samples from anemia and trait patients were exposed to low oxygen tension in O_2 N_2 mixtures the following results were noted (1) In an atmosphere of 2 per cent oxygen there was increased sickling of cells in four of six specimens from sickle cell anemia but not in trait erythrocytes (2) All specimens showed definite increase of sickling in pure nitrogen (3) At any given oxygen tension degree of sickling for anemia cells was greater than for trait erythrocytes (4) Mechanical fragility of both types of cells increased with increase in number of sickled form Addition of 10% carbon dioxide to the O N_2 gas mixtures lowered the pH of specimens to 663 708 and produced sickling of both types of cells in higher oxygen concentra tions Sickle cell anemia erythrocytes tended to assume their abnormal shape at distinctly higher oxygen tension than trait cells although there was some overlapping (Fig 55) In general oxygen tension had to be reduced to a partial pres sure of 15 mm Hg or less before appreciable sickling of trait cells occurred Addition of buffers to the various ex perimental gas mixtures demonstrated that it was pH rather than presence or absence of carbon dioxide which influenced

(8) J Lab & Cl Med 37 789 80 M y 1951

intracorpuscular erythrocyte defect comparable to sickle cell anemia

Subjects with hemoglobin III and normal hemoglobin had no symptoms of anemia or hemolytic process and no unusual physical findings The only morphologic abnormality was presence of numerous target cells in fixed blood films Resistance of red cells to hypotonic saline was increased in two subjects and normal in one There was no apparent cor relation between osmotic resistance and the number of target cells Unexpectedly survival of patients red cells was notably shortened in normal subjects This behavior of red cells from persons without demonstrable hemolysis was unique Results of direct and indirect Coombs tests were negative

This syndrome seems to be midway between asymptomatic sickle trait and sickle cell anemia but is distinguishable from both on genetic chemical hematologic and clinical grounds the latter being the benign course with mildness of anemia and progressive enlargement of the spleen Preliminary studies with fractional alkaline denaturation indicate a similarity between hemoglobin III and thalassemia hemo globin But on hematologic grounds the relation is not ap parent

Acute Erythroblastopenia in Sickle Cell Anemia and Infectious Mononucleosis The precipitous drop in red cell count and hemoglobin values noted in hereditary spherocytosis and familial hemolytic icterus has been called aplastic crisis The pathophysiologic mechanisms have been extensively dis cussed and no evidence of hypersplenism either in inhibiting marrow or causing increased hemolysis was thought to be present A similar phenomenon in hematologically normal persons was first shown by Gasser in various infectious and allergic diseases Whereas in patients with hemolytic anemia striking drop in red cell count occurs in hematologically normal persons only minimal fall of red cell and hemoglobin levels results

Because of high incidence of sickle cell anemia in some areas relatively frequent aplastic crises have been predicted Amoz I Chernoff and Aaron M Josephson[1] (Chicago) dis cuss five patients four with sickle cell anemia and one with infectious mononucleosis

(1) A M A Am J D Ch ld 82 310 32 S pt mb 1951

when a number of patients suspected of having sickle cell anemia presented a hemolytic syndrome associated with erythrocytic sickling and splenomegaly in whom neither clinical hematologic nor genetic patterns fitted typical sickle cell anemia Using electrophoretic analysis the authors discovered a new hemoglobin component clearly distinguishable from normal and sickle cell hemoglobin called hemoglobin III The combination of hemoglobin III with sickle cell hemoglobin is associated with a mild hemolytic syndrome In combination with normal hemoglobin it produces an asymptomatic carrier state without sickling The homozygous condition with respect to hemoglobin III has not yet been recognized

Five patients in each of two families were studied The condition was discovered in both families because of the coincidence in some of the children of sickling and a hemolytic anemia One parent in each family had the new component mixed with normal hemoglobin the other had typical sickle cell trait with normal and sickle cell hemoglobin Three types of offspring were produced those with (1) a combination of sickle cell hemoglobin and hemoglobin III (2) a mixture of hemoglobin III and normal hemoglobin and (3) only normal hemoglobin Hemoglobin III like sickle cell hemoglobin is transmitted as a simple mendelian dominant The precise relation of this gene to that responsible for sickling is not yet clear

The subjects with hemoglobin III and sickle cell hemoglobin invariably had sickling phenomenon in vitro in sealed wet preparations resembling sickle cell anemia rather than sickle trait In dry stained blood films numerous target cells were noted again resembling classic sickle cell anemia Otherwise red cell morphology was remarkably normal with only slight reticulocytosis The number of siderocytes (red cells with iron staining inclusions by prussian blue technic) was not increased in contrast to the findings in most sickle cell anemia patients Resistance of red cells to hypotonic saline was significantly increased Only mild hemolytic disturbance was demonstrable with slight to moderate elevation of reticulocytes serum bilirubin and fecal urobilinogen excretion Survival of normal red cells transfused into two patients was normal but survival of cells from either patient transfused into normal recipients was notably shortened indicating an

Hereditary Spherocytosis II Observations on Role of Spleen Because splenectomy decrea es destruction of red cells in hereditary spherocytosis Lawrence E Young Richard F Platzer Donald M Ervin and Mary Jane Izzo investigated action of the spleen on these defective cells O motic and mechanical fragility of donated and patient s cells in peripheral venous and postoperative splenic blood were determined by a differential serologic technic in three patients with hereditary spherocytosis and in a girl 15 with pancytopenia and multiple congenital abnormalities (Fanconi s syndrome) None was in crisis at the time of the studies

The relatively large proportion of patient s cells in splenic as compared to venous blood indicated that spheroidal cells were selectively retained in the spleens of the three patients with spherocytosis whereas the difference in the patient with Fanconi s syndrome was not significant The splenic tissue in spherocytosis was engorged with red cells most of which were in the pulp whereas the venous sinusoids were relatively empty Red cells were not numerous in the spleen of the patient with Fanconi s syndrome

In the three cases of spherocytosis osmotic fragility of spheroidal cells trapped in the spleen was greatly increased in contrast with the donated cells but in venous blood was only slightly greater Mechanical fragility of donated cells in venous blood drawn after transfusion but before splenectomy was not increased it was increased in patients cells to the same extent as before transfusion Measurements of dif ferential mechanical fragility of donated and patients cells in splenic mince blood were unsatisfactory

The curve for patient s cells in Fanconi s syndrome was almost identical with that obtained before transfusion where as that for donated corpuscles was within normal limits These results show that nonspheroidal cells were not selectively trapped in the spleen and that fragility of the few such cells in the postoperative spleen had not increased In this case proportion of donated corpuscles in the splenic blood was nearly the same as in venous blood In the spherocytic cases this proportion was relatively small even though the cells had been given four to eight days before splenectomy

Results in a patient with mild icterus spherocytosis

(2) Blood 6 1099 1113 N mbe 1951

CASE 2—Negro girl 5 with known sickle cell anemia was hospitalized with listlessness anorexia elevated temperature and vomiting Temperature and pulse rate above normal and mild lymphadenopathy and enlargement of tonsils were found Urine contained acetone Red cell count was 1 500 000 white cell count 6 100 and hemoglobin content 4 33 Gm One nucleated red cell/100 white cells and *numerous target and sickle cells* were present. There were no reticulocytes or polychromatophilia Coombs test results were normal Marrow erythrocyte granulocyte (E G) ratio was 1 12 2 She was treated with antibiotics and blood Extensive bacteriologic and serologic studies gave essentially normal result On the 4th day pronormoblasts and basophilic normoblasts increased and on the 6th day E G ratio was 3 6 1 Reticulocytes reappeared in the peripheral blood on the 6th day and reached 13% on the 11th day

Though no single etiologic agent can be blamed for this condition its frequent association with allergic and infectious (especially viral) processes is more than coincidental Since marrow aspirations are not routine in hematologically normal persons such reactions will be missed The common factor in most cases is striking disappearance of most red cell precursors except a few pronormoblasts The phase of marrow erythroblastopenia may last 10 days When regeneration starts reticulocytes may be expected within four days

The effect of arrest of red cell production depends on presence of hemolytic anemia Normal red cells live about 120 days and the count remains constant by balanced delivery and disintegration rates Decreased delivery causes decreased count which is slight in normal patients (1%/day) Such a decrease even for 10 days is within limits of laboratory error If disintegration rate increases as in hemolytic syndromes there is dramatic decrease in red cells In sickle cell anemia red cells survive only 15 60 days Since red cell count usually remains constant delivery must be increased (marrow hyperplasia and reticulocytosis) Sudden cessation of delivery would rapidly decrease red cell and hemoglobin values Severity of anemia depends on its duration and survival time of the patient s red cells

Diagnosis is suspected if there is no polychromatophilia confirmed by marrow aspiration Without hemolytic anemia however the *striking features of the crisis are lacking Treat*ment of aplastic crisis requires vigorous use of transfusions as well as specific therapy of the underlying disease —

the cells in splenic mince blood in greater amounts than in perfused mixtures In a control perfusion with a mixture of 2 normal bloods the proportions of the two types of cells in the splenic vein and in splenic mince blood did not alter Sections of spleens taken before perfusion contained relatively few red cells whereas those prepared after perfusion with spherocytes showed packing of red cells in the pulp as had been seen in spleens from patients with hereditary spherocytosis

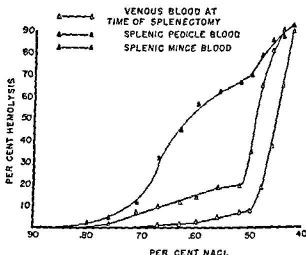
The authors believe that spheroidal cells are trapped in splenic pulp because their abnormal thickness prevents easy escape through slitlike openings into venous sinusoids Cells stagnating in the pulp are removed from the protective factors in circulating blood and osmotically active substances accumulate in the cell Some cells with increased thickness do escape and probably account for the tails of fragility curves obtained with blood from the splenic vein and with peripheral blood of patients with intact spleens These are thought to be relatively susceptible to destruction by wear and tear Many cells remaining in the spleen undergo lysis so that evidence of phagocytosis of whole red cells in the spleens of such patients is not striking The exact nature of the red cell abnormality in this disease and of the changes in these cells when sequestered or incubated in vitro is not clear Pathogenesis of crises in these patients also remains a mystery

Viremia in Acute Hemolytic Anemia and in Autohemagglutination Report of Case and Review of Literature with Special Reference to Virus of Newcastle Disease The virus of Newcastle disease an acute and highly fatal infection in various species of birds has been isolated in only 10 recorded cases in man Most mammals are highly resistant to potent laboratory strains of the virus hamsters mice and monkeys are the only animals to have been successfully infected in the laboratory

Sylvan E Moolten and Ellen Clark[3] (New Brunswick N J) report a case in which the virus was isolated from the blood of a woman 37 shortly after subsidence of acute hemolytic anemia with autohemagglutinative vascular phenomena During active stages of the illness the patient had an eruption resembling that of acute disseminated lupus erythematosus

(3) A M A A h I t M d 89 270 292 F bru ry 195

reticulocytosis and splenomegaly without anemia are shown in Figure 56 The tail of the osmotic fragility curve largely disappears after splenectomy in such patients This observation together with the larger 'tail in the curve for splenic vein blood suggests that cells most susceptible to lysis in hypotonic saline solution may be those that have passed through the spleen after being imprisoned for a time in the splenic incubator Curves for cells from splenic pulp



F g 56—O moti f ag l ty cur e bta ed w th eryth ocyt s in sample of blood f om m ed sple n spl c e n and antecub tal v n f p t nt w th he ed t ry pherocytos s who nd rwe t plenectomy w tho t ba g b e transf sed. (C u t y of Yo g L E *et l* Blood 6 1099 1113 No mber 1951)

(mince blood) reveal greatly increased fragility of a large proportion of corpuscles and are similar to curves obtained when peripheral blood from patients with hereditary spherocytosis (either pre or postsplenectomy) is incubated in vitro at 37 C for 24 hours

Perfusion studies with mixtures of normal and spherocytic blood which could be differentiated serologically were done with spleens from four patients with idiopathic thrombocytopenic purpura In each instance proportion of spheroidal cells emerging from the splenic vein became less and that of normal cells greater during perfusion Selective trapping of spherocytes in the spleen was confirmed by demonstrating

Cortisone and corticotrophin produced temporary clinical im provement followed by relapse during administration

Similarities between the acute hemolytic syndrome of this and other cases suggest the possibility that hemotoxic viruses may be commoner than ordinarily suspected as a cause of acute hemolytic anemia The authors assembled data (table) which appear to indicate that acute hemolytic anemia and hemagglutinative syndromes complicating Hodgkin s disease leukemia lymphosarcoma and other widespread diseases of the reticuloendothelial system may result from the multipli cation of latent viruses owing to impaired resistance Nutri tional deficiencies may play a similar role

Acute hemolytic anemia in some infections might represent a multiple type of immune response to a specific viral or other infective antigen Equally plausibly autoantibodies for red cells might be produced as a consequence of intravascular hemolysis by the infective agent in the course of which structure of the erythrocyte is modified sufficiently to render it antigenic Another possibility is that a person infected with a hemotoxic virus such as mumps or Newcastle disease virus may develop sufficient antiviral immunity to bring about autoagglutination as the effect of antiviral antibodies on virus sensitized red cells Such red cells might be expected to possess an antibody coating demonstrable by the Coombs antiglobulin test

Based on these considerations it is possible that certain cases of hemolytic anemia in which results of the Coombs test are positive may be instances of infection with hemotoxic virus in which the virus or a noninfective viral residue or hemagglutinating component plays the part of a go between linking antiviral immune bodies to red cells In the authors case a negative Coombs antiglobulin reaction was accompanied by a positive antialbumin reaction suggesting that serum albumin was nonspecifically adsorbed on the cells as a result of viral injury or other hemotoxic agent In these circum stances Coombs serum containing antialbumin antibodies could give falsely positive agglutinations

Examination of the blood for viruses may be warranted when resistance to infection is impaired particularly when complicated by hemolytic or hemagglutinative phenomena or

Correlation between Autohemagglutination and Occurrence of Hemagglutinating Viruses in Blood

Diagnosis	Autoag utination at Room Temp	Antialbumin	Antiglobulin	Virus Isolation	V rus Hem g lu na on	V u H m
Acute hem anemia	++++	++	—	Pos N D V†	Pos	Pos
N D V contact	++	++	±	Pos N D V	Pos	Pos
N D V contact	++	+	+	——		
Convulsive encephalopathy N D V contact	++	++	—	Pos N D V	Po	Pos
Monocytic leukemia with acute hem anemia	+++	+	—	Pos N D V	Pos	Po
Leukemia	+	+	+	Pos unidentified	Pos	Pos
Leukemia	+++	+	—	Pos unidentified	Pos	Pos
Leukemia	—	+	++	Pos unidentified	Pos	——
Hodgkin s disease	+	+	±	Pos unidentified	Pos	Pos
Hodgkin s disease	+	++	+	Pos unidentified	Pos	Po
Recurrent urticarial purpura with vesication	+	+	±	Pos herpes simplex	Pos ‡	None
Generalized herpes simplex	±	+	+	Pos herpes simplex	Pos ‡	None
Ulcerative colitis	++++	+	—	Pos herpes simplex	Pos ‡	None
Diss lupus erythematosus	+	±	—	Pos unidentified	Pos	— —
Acquired hem icterus	+++	+	—	Pos unidentified	Pos	Pos
Hem anemia of pregnancy	+	++	+	Pos unidentified	Pos	Pos
Atypical pneumonia	++	+	+	——	—	——
Carcinoma ?	++	+	+	— — —	—	—

I utoaggl t at n t te + q 1 1 4 ++ 1 16 +++ 1 64 ++++ 1 256

† Newca tl d ea e rus

‡ Only t 37 C

natural antihuman red cell antibody (2) cold hemagglutinins sometimes present in the patient s serum sensitize red cells for the antiglobulin reaction the Donath Landsteiner antibody of paroxysmal cold hemoglobinuria may sensitize red cells in Coombs reaction [This last however is not a false positive strictly speaking but only an example of detection by the Coombs test of another type of antibody than that found in the patients under discussion —Ed]

Any antibody present in the patient s serum may agglutinate normal compatible red cells in albumin normal serum or plasma or trypsinized red cells in saline solution and may sensitize normal erythrocytes for the antiglobulin reaction This must be differentiated from specific immune isoantibodies such as anti Rh which are especially prone to develop after transfusion of patients with this disorder Therefore in initial screening it is preferable to demonstrate the antibody on the red cells and to postpone tests on serum until the second round of investigation

Most important is differentiation of this disease and congenital hemolytic anemia (hereditary spherocytosis) Spherocytosis and increased osmotic and mechanical fragility are constant features of the latter but they are usually noted in autoimmune disease only during great hemolytic activity Autoantibody is usually absent in the inherited disease Since autoantibody can react with all human red cells normal transfused erythrocytes show sphering and increased fragility and are rapidly destroyed in the circulation of patients with autoimmune hemolytic disease Normal red cells transfused to patients with hereditary spherocytosis usually undergo no demonstrable change and survive normally Thrombocytopenia is seen often and leukopenia occasionally in this disease It has been suggested that platelets may be destroyed by antibody and that there may be a spectrum like relation between idiopathic thrombocytopenia and acquired hemolytic anemia

The chances of benefit from splenectomy are great enough to justify surgery in most cases Remission of anemia often follows although some production of antibody continues and relapse may occur at any time which indicates that the spleen is not solely responsible for the disease ACTH and cortisone have induced striking deceleration of red cell destruction but

manifested as atypical vascular symptoms such as Raynaud s syndrome or acrocyanosis

[This report if confirmed is of very great interest In addition the article contains an extensive review of literature and bibliography —Ed]

Clinical and Laboratory Observations on Autoimmune Hemolytic Disease are presented by Lawrence E Young Gerald Miller and Richard M Christian[4] (Univ of Rochester) The term acquired hemolytic anemia has been applied to patients in whom antibodies have developed which have reacted with the red corpuscles These antibodies the origin of which is unknown usually develop independently but may occur with many diseases especially leukemia the lymphomas carcinomatosis Boeck s sarcoid tuberculosis and lupus erythematosus Serologic red cell abnormalities in idiopathic cases are indistinguishable from those in so called symptomatic cases Presence of autoantibody active at body temperature is the *sine qua non* of the hemolytic disorder Methods of demonstrating the antibody attached to the red cells of the patient are agglutination of red cells by antiglobulin rabbit serum (direct Coombs test) agglutination of red cells when suspended in a mixture of albumin and normal human serum and elution of antibody from red cell stroma and subsequent adsorption on normal red cells Methods of demonstrating the autoantibody in the patient s serum are agglutination of normal compatible red cells suspended in albumin or normal human serum agglutination of trypsinized normal compatible red cells suspended in saline solution and sensitization of normal compatible red cells for the antiglobulin reaction by exposure especially at pH 6 8 to patient s serum (indirect Coombs test)

Some causes of false negative Coombs reactions are weak rabbit serum prozone phenomenon i e cells tested with inadequately diluted serum may fail to agglutinate even though coated with antibody red cells insufficiently washed i e adherent nonspecific globulin may neutralize the antiglobulin antibodies and prevent their reaction with specific erythrocyte bound autoantibodies when red cells are mixed with antiglobulin antibodies Some causes of false positive reactions are (1) rabbit serum incompletely absorbed with normal human red cells i e rabbit serum still contains

(4) Ann. Int M d. 35 507 517 S ptemb 1951

globinuria was chilled and warmed with complement and homologous or heterologous erythrocytes and leukocytes erythrophagocytosis occurred it reached a maximum at a time consistent with development of leukopenia in vivo Although the paroxysmal cold hemoglobinuria antibody was fixed to erythrocytes in the cold phase of the Donath Landsteiner reaction phagocytosis did not occur if complement with the attending hemolysis was absent in the warm phase Erythrophagocytosis was also produced in vitro when isoantibodies from man acted as either agglutinins or hemolysins for normal red cells Phagocytosis was most pronounced when the sensitized cells were lyzed degree of phagocytosis corresponding to that of hemolysis

Observations suggested that leukopenia occurs in persons with cold hemoglobinuria as part of the paroxysm of hemolysis and that erythrophagocytosis operates to remove damaged erythrocytes and probably promotes trapping of leukocytes in organ capillaries

[The reader should appreciate that the demonstrable hemolytic system rather than erythrophagocytosi i probably the major mechanism of red cell destruction —Ed]

Acute Hemolytic Anemia Due to Ingestion of Naphthalene Moth Balls is reported by James V Mackell Fredric Rieders Heinrich Brieger and Edward L Bauer[6] (Jefferson Med College)

Negro boy 18 months was hospitalized after 24 hours of palmar pallor frequent crying passage of dark red urine anorexia and fainting spells Later it was learned that he had played with moth balls five days before He was acutely ill the sclerae were icteric and liver edge was 3 cm below the costal margin Blood studies showed hemoglobin content at 2 6 Gm red cell count 870 000 reticulocytes 12 2% white cell count 63 000 platelets 438 000 and serum bilirubin at 5 3 mg /100 cc No Heinz bodies were seen with brilliant cresyl blue stain Tests for sickling and red cell fragility showed normal re ults Urine had an odor of moth balls and chemical analyses revealed large amounts of alpha naphthol until the 12th day Whole blood transfusions were given and he recovered and was di charged in 30 days

Chemical and spectrophotometric studies of urine revealed alpha naphthol beta naphthol alpha naphthoquinone and beta naphthoquinone experiments were run to determine the relative hemolytic activity of the metabolites and of the naphthalene itself

(6) P d t 7 72 728 M y 1951

lengthy remissions are unusual These drugs may be of value in preparing acutely ill patients for splenectomy Nitrogen mustard irradiation of lymph nodes and other therapy directed at an underlying disease may also be beneficial in the symptomatic type Transfusions are necessary in severe anemia but may accelerate the hemolytic process Cross matching is often difficult because the autoantibody may react with donor red cells and be confused with specific isoantibodies There is no rationale for use of iron compounds liver extract multiple vitamins or shotgun preparations

The authors recommend that a high index of suspicion be maintained for *autoimmune hemolytic disease* especially in patients with refractory anemia persistent reticulocytosis hemoglobinemia hemoglobinuria mild icterus or splenomegaly Continuing search should be made for an underlying disorder once the hemolytic process has been demonstrated Moreover the natural fluctuating course of the disease with its spontaneous remissions should be considered in evaluating response to any therapeutic regimen

Mechanism of Hemolysis in Paroxysmal Cold Hemoglobinuria III Erythrophagocytosis and Leukopenia William S Jordan Jr Robert L Prouty R W Heinle and John H Dingle[5] (Western Reserve Univ) induced attacks of hemoglobinemia in two patients with paroxysmal cold hemoglobinuria Occurrence of slight neutropenia and erythrophagocytosis in the first patient occasioned more detailed observations of these phenomena in the second The *in vivo* changes observed in the latter after three episodes of chilling were similar to those described by earlier investigators Pronounced hemoglobinemia and hemoglobinuria were noted twice mild hemoglobinemia once The maximal number of phagocytes was observed at the time of maximal hemolysis Leukopenia developed promptly during each attack but degree of leukopenia was not correlated with either intensity of erythrocyte destruction or extent of phagocytosis Neutrophils and monocytes—the phagocytic cells—and eosinophils were equally depressed all decreasing by 75 80% Lymphocytes decreased by 33-48% Neutrophils recovered within two hours but eosinophils and lymphocytes remained depressed for five

When serum from patients with paroxysmal cold hemo

(5) Blood 7 387 407 Apr 1 195

dice and in part in cirrhosis and in an instance of ovarian cyst A more acute picture has been reported following primary atypical pneumonia Etiology is unknown Cold agglutinins are somehow involved in immunity mechanisms and have frequently shown raised titers in such infections as trypanosomiasis primary atypical pneumonia and possibly malaria Rise and fall of titer in primary atypical pneumonia resembles an immune antibody reaction

Cold agglutinins are found in serum gamma globulin and in low titer also in many normal people The syndrome may therefore result from some obscure disturbance of immunity mechanisms causing appearance of normal antibodies in greatly enhanced titers Raynaud s phenomena are almost certainly due to obstruction of the peripheral circulation by autohemagglutination in vivo Relative importance of cold agglutinins perhaps acting to increase the destruction of red cells by mechanical effects due to the buffeting of the circulation and hemolysins in causing hemolysis in vivo is less clear Dacie has demonstrated cold hemolysins to be present on acidification of the serum whenever cold agglutinins were present in high titer

Cold agglutinins are antibodies produced to some extent by the spleen splenectomy although not yet tried in this condition might help by removing a site of production and also an organ which filters damaged cells from the circulation Apart from splenectomy patients should occupy warm rooms especially in winter and dress warmly ACTH tried briefly in one reported instance gave no apparent benefit

The authors point out that the patients form a homogeneous group unlike other types of hemolytic anemia (especially syphilitic cold hemoglobinuria) because of distinctive clinical and laboratory findings they review nine similar cases from the literature

Treatment of Acquired Hemolytic Anemia With Note on Relationship of Periarteritis Nodosa to Hemolytic Anemia William Dameshek and Martin C Rosenthal[8] (Tufts College) note that hereditary hemolytic anemias (spherocytic leptocytic sickle cell) are associated with an inherited intrinsic defect of the erythron In contrast in acquired hemolytic anemia normal transfused red cells are attacked by an ex

(8) M Cl N rth Am 35 14 3 1440 S pt mbe 1951

METHOD —Suspensions of each material and 1 5 1 10 1 50 1 75 and 1 100 dilutions were prepared with normal saline Blood specimens from healthy human donors were heparinized and hemoglobin and methemoglobin content was measured they were used within ½ hour after drawing against each compound in every dilution

In series I 5 cc blood was mixed with 1 cc of the agents refrigerated at 2 C for three hours and the plasma which had separated was withdrawn and analyzed for its hemoglobin content

In series II plasma obtained by centrifugation was mixed with 1 cc of the agents the cells were reintroduced and the mixture treated as in series I

In series III the red cells were washed three times with saline then mixed with 2 cc of the agents and incubated at 2 C for three hours The clear supernatant fluid was analyzed for hemoglobin

In series IV 100 mg of both cholesterol and lecithin was shaken with 5 cc of the agents After centrifugation 2 cc of supernatant liquid was used on washed red cells as in series III

In series V 1 2 4 and 5 cc of each agent was injected into the ears of white male rabbits At 2 5 and 15 minute intervals 5 cc of freely flowing blood was obtained centrifuged and the plasma then analyzed for hemoglobin

Naphthalene showed no hemolytic activity but in vitro studies revealed that the hemolytic activity of the metabolites decreased in the following order alpha naphthol beta naphthol alpha naphthoquinone and beta naphthoquinone When given intravenously to rabbits only alpha naphthol was hemolytic 6% hemolysis being obtained with 4 cc and 9% with 5 cc (1 mg/cc) Methemoglobin was not formed in any of these experiments Plasma cholesterol and lecithin did not inhibit hemolytic activity of naphthalene metabolites in vitro

Association of Raynaud s Phenomena, Chronic Hemolytic Anemia and Formation of Cold Antibodies in three cases is reported by D G Ferriman J V Dacie K D Keele and Jane M Fullerton [7] Hemoglobinuria on exposure to cold occurred in two patients and probably in the third and the serum contained cold agglutinins cold hemolysins and incomplete cold antibodies in considerable titer In each instance intra vascular hemolysis with resultant local hemoglobinemia was provoked by experimental cooling of a limb

This syndrome has been reported with or without hemoglobinuria in leukemia malaria and congenital acholuric jaun

(7) Quart. J Med. 20 275 9 July 1951

traindications should be disregarded If maximal effect is achieved maintenance dosage of cortisone orally usually 50 100 mg is continued as long as circumstances require it If maximal effect does not result dosage may be increased to development of Cushing s syndrome

Splenectomy is the choice when all other methods have failed but it is usually curative only in hypersplenic hemo lytic anemia Removal of ovarian and other tumors is some times beneficial and may be tried if hemolysis continues

[In our experience ACTH and cortisone are usually of greatest value in preparing the patient for splenectomy When splenectomy fails to produce substantial improvement or a relapse occurs smaller doses of cortisone may be useful —Ed]

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

The first two articles serve to orient the reader to the nature of the various deficiencies responsible for these macrocytic anemias and of the mechanisms that may create them —Ed

Pathogenesis of Megaloblastic Anemias L J Witts[9] (Radcliffe Infirm Oxford) states that the megaloblastic anemias can be arranged in a spectrum with addisonian per nicious anemia at one end responding to vitamin B_{12} and pernicious anemia of pregnancy at the other responding to folic acid In between are the megaloblastic anemia of infancy nutritional macrocytic anemia the various types of steator rhea intestinal macrocytic anemia and achrestic anemia Vitamin B_{12} B_{12b} B_{12} and B_{12d} appear to be equally effec tive in pernicious anemia although they differ in their effects on micro organisms The folic acid group includes pteroylglutamic acid its conjugates and its derivative folinic acid There is no chemical relation between vitamin B_{12} and folic acid Tissue assay of biopsy and autopsy samples has shown that in pernicious anemia the organism is depleted of vitamin B_{12} and to some extent of folic acid In the macrocytic anemia of steatorrhea there is more severe depletion of folic acid but no data have been published on vitamin B_1 In per nicious anemia feces contain vitamin B_{12} and folic acid in amounts which would be equivalent to a therapeutic dose if they were capable of absorption In the large intestine how

(9) Lancet 2 367 369 Sept 1 1951

trinsic mechanism usually an abnormal red cell antibody which also attacks the patient s own red cells (both iso and auto in type)

There are three main acquired types (1) Increased hemolysis is induced by direct action on red cells of such chemicals as sulfanilamide and saponin and such physical agents as extreme heat or cold (2) Some agent (infection chemical neoplasm or leukemia) causes development of autoimmunization and an autoantibody which attacks the patient s cells Usually the fundamental cause is obscure and the disorder is labeled idiopathic but when the cause is found cases are called symptomatic Symptomatic cases are usually associated with such lymphoid proliferation as leukemia and lymphosarcoma (3) Red cells are injured by some unusual splenic or hypersplenic mechanism

Findings include pallor slight icterus splenomegaly anemia and indirect bilirubinemia variable degree of spherocytosis and increased polychromatophilia Morphologic spherocytosis is not pathognomonic of inherited hemolytic anemia since the hereditary and acquired spherocytes are superficially identical Immunologically they differ in that the acquired type have an adsorbed coating of abnormal antibody from the blood whereas the hereditary spherocyte is intrinsically defective with a surface membrane uncoated with antibody The antibody coating can be detected by the Coombs antiglobulin serum The possible association of this condition with periarteritis nodosa is of particular interest in view of the widespread use of penicillin and other antibiotics and the possible development of both a vascular allergy and an immunohemolytic process

Fresh whole well typed blood should be used in transfusions with particular attention to typing and the patient s condition during and after transfusion The plasma transfusion reaction is treated with washed red cells Blood should not be given too fast or too often If few transfusions are ineffective multiple transfusions are not likely to halt the process

ACTH or cortisone should be started in relatively high dosage with due regard for therapeutic contraindications Since the hemolytic process is often of immediate seriousness outweighing all other considerations minor therape con

glutamic (folic) acid and folinic acid Most hematologists believe that the extrinsic factor is B_{12} the intrinsic factor promotes intestinal absorption of B_{12} and the major anti pernicious anemia factor in liver extracts is B_1 The diet normally contains B_1 folic acid or its conjugates and folinic acid Urine of normal persons and those with pernicious anemia contains traces of all three Unconfirmed evidence suggests that folinic acid is the final antimegaloblastic substance Chemically it is related to folic acid but its structural formula is not yet known Girdwood uses Lactobacillus leichmannii in microbiologic assays for B_{12} Streptococcus fecalis for folic acid and Leuconostoc citrovorum for folinic acid

Megaloblastic anemia is believed to occur if the diet is deficient in B_1 or folic acid conjugates The reason for the high loss of these factors during cooking is not known although possibly they are bound in various tissue combinations Daily intake of folic acid is probably 1 mg or less Indirect evidence suggests that though folic acid may at first be effective in pernicious anemia both B_1 and folic acid must be present for continued normoblastic formation Vitamin B_{12} by mouth will not normally act in pernicious anemia unless in very high dosage or unless normal ga tric juice or other intrinsic factor source is given simultaneously

Certain bacteria synthesize B_{12} and folic acid and probably folinic acid and others destroy the e factors In pernicious anemia abundant flora extends up the small intestine into the stomach If folic acid or folinic acid were synthesized in sufficient amounts where absorption is possible megaloblastic anemia would not occur but since folic acid does not prevent subacute combined cord degeneration it might occur even with relatively high red cell levels If enough B_{12} were synthesized in patients with intrinsic factor it could be absorbed and might prevent megaloblastic anemia If organisms destroyed folic acid or B_1 or rendered intrinsic factor unavailable this might explain variations in anemia seen in India and Burma during World War II Vitamin B_{12} presumably from bacterial synthesis found in the feces of a pernicious anemia patient produced hemopoietic response on injection in a similar patient In support of this observation by Bethell Girdwood assayed intestinal contents at various levels in control and pernicious anemia patients for B_{12} folic

ever they probably play little or no role in the body economy

Although knowledge of hematinic principles has advanced greatly comparable progress has not been made in determining conditions in the gastrointestinal tract which govern their absorption in active form or conditions in the body which govern their activity Usually simple atrophy of the mucosa of the body of the stomach has been found in pernicious anemia and diffuse inflammatory gastritis in other forms of achlorhydria Anatomic changes in the stomach and intestine are absent in other megaloblastic anemias There is ample evidence that an intrinsic factor in gastric juice interacts with vitamin B_{12} in the diet and somehow promotes intestinal absorption In pernicious anemia absolute failure of gastric secretion is less common than was previously thought and special procedures have shown that appreciable amounts of free acid and pepsin may be secreted when other test results suggest achlorhydria or achylia If even 10 cc gastric juice may ensure absorption of adequate vitamin B_1 sensitive tests must be used before deciding that gastric juice is not being secreted [in physiologically active amounts —Ed]

Megalocytic anemia cannot be produced by gastric resection in animals and pernicious anemia does not always occur after such resection in man But megalocytic anemia and subacute combined degeneration occasionally follow intestinal stenosis or formation of stagnant intestinal loops in man when gastric secretion seems normal Study of experimental macrocytic anemia of intestinal culdesacs in laboratory animals has suggested that intestinal bacteria affect absorption or requirements of vitamin B_{12} and folic acid It has been proposed that gastric changes may result partly from a deficiency caused by abnormal bacterial activity in the small intestine a vicious circle being formed which leads to pernicious anemia Little is known however of the factors determining absorption and activity of folic acid and vitamin B_1 or their inter relation in formation of blood cells

Vitamin B_1 and Folic Acid in Megaloblastic Anemias Ronald H Girdwood[1] (Univ of Edinburgh) states that the main unsolved problems of megaloblastic anemias concern (1) the precise metabolic disorder which produces megaloblastosis and (2) the inter relation of vitamin B_1 oteroyl

(1) Ed b rgh M J 58 309 335 J ly 1951

glutamic (folic) acid and folinic acid Most hematologists believe that the extrinsic factor is B_1 the intrinsic factor promotes intestinal absorption of B_{12} and the major anti pernicious anemia factor in liver extracts is B_1 The diet normally contains B_{12} folic acid or its conjugates and folinic acid Urine of normal persons and those with pernicious anemia contains traces of all three Unconfirmed evidence suggests that folinic acid is the final antimegaloblastic substance Chemically it is related to folic acid but its structural formula is not yet known Girdwood uses Lactobacillus leichmannii in microbiologic assays for B_{12} Streptococcus fecalis for folic acid and Leuconostoc citrovorum for folinic acid

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and folinic acids (table) The significance of these findings is difficult to assess The daily stool output is about 3 μg B_{12} and 0 5 μg folic acid

If antibiotics do not act as or cause absorption of hemopoietic factors theoretically they may improve a pernicious anemia patient by destroying organisms which antagonize or use up hemopoietic factors or make him worse by preventing bacterial synthesis Hemopoietic response to aureomycin in pernicious anemia and nutritional megaloblastic anemia and to penicillin in the latter anemia has been reported

Significance of urinary hemopoietic factors is uncertain

MEAN CONTENT OF GROWTH FACTORS FOR L LEICHMANNII AND STREP FECALIS IN ALIMENTARY TRACT OF FASTING PATIENTS

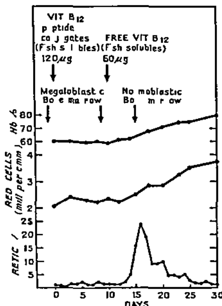
Specimen	Growth Factors for L leichmanni (Chiefly Vitamin B_{12}) μg /ml		Growth Factors for Strep fecalis (Folic and Folinic Acid) μg /ml	
	Pernicious Anemia (3 Patients)	Controls (2 Patients)	Pernicious Anemia (3 Patients)	Control (1 Patient)
Gastric juice	0 005	0 004	0 071	0 039
Duodenal contents	0 003	0 0009	0 037	0 057
Jejunal contents	0 003	0 005	0 042	0 011
Ileal contents	0 004	0 001	0 404	0 067
Feces (μg /Gm) dried	0 127	0 089	12 1	1 1

although small amounts of folic acid and B_{12} are found in normal persons and those with pernicious anemia and sprue Such figures are approximate Moreover when a normal or anemic person is given an injection of one of these substances part is excreted in the urine usually within 24 hours Even normal persons given extremely large doses of B_1 orally excrete only traces in the urine

In the past spontaneous remissions were sometimes seen in pernicious anemia Many substances can produce hematologic responses Vitamin B_1 differs from forms B_{1b} B_{1c} and B_{12d} by containing a cyano group Megaloblastic anemia usually responds to folic acid but should not be used in pernicious anemia because it will not prevent and may hasten onset of subacute combined degeneration Synthetic folinic acid was used to treat three relapsed pernicious anemia patients with good clinical and hematologic response to a single injection of 12 16 mg but only slight response to 6-8 mg or less Vitamin B_{12b} can be converted to B_1 by treatment with hydrogen cyanide and if sodium cyanide is added to

liver extract more B_{12} is obtained by assay This may explain low B_1 values found in liver in the past by microbiologic assay

Hemopoietic Effect of Vitamin B_{12} Prepared from Fish After autoclaving and pressing gutted fish and condensing the resultant juice (fish solubles) K Hausmann and K Mullr[2] (Hamburg) extracted cobalt containing red pigments which



F g 57 — H mopo t ff ct f t m n B_{12} p p d f m fish pat t w th pe em (Cou t y f H m nn K d M ll K La t 1 185 188 J 26 195)

by microbial assays had a high vitamin B_1 potency After the material with potassium cyanide added had been left standing for eight days the red pigments became completely soluble in butanol and showed the absorption spectra of vitamin B_1 Samples of each preparation were given parenterally to 3 patients with true pernicious anemia in single doses equivalent to 50 and 60 µg vitamin B_1

(2) La t 1 185 188 J 26 1952

and folinic acids (table) The significance of these findings is difficult to assess The daily stool output is about 5 μg B_{12} and 0 5 μg folic acid

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synthesis this material is not present in the actively absorbing portion of the bowel and in the patient with pernicious anemia would not be absorbed in any case because of the lack of gastric secretion —Ed]

Observations on Absorption, Utilization and Excretion of Vitamin B_{12} Present evidence suggests that pernicious anemia is a vitamin B_{12} deficiency state attributable to im paired absorption of the vitamin from the gastrointestinal tract Recent studies showed that vitamin B_{12} activity of the urine negligible in normal subjects and pernicious anemia pa tients promptly increased after parenteral administration of 100 μg of the vitamin However when single doses up to 500 μg were given orally there was no measurable increase even in controls This suggests that vitamin B_1 may be poorly absorbed from the normal gastrointestinal tract

C Lockard Conley Julius R Krevans Bacon F Chow Charles Barrows and Calvin A Lang[4] (Johns Hopkins Univ) gave varying amounts of vitamin B_{12} orally intramuscularly and intravenously to normal persons and pernicious anemia patients and estimated the urinary excretion rate Striking improvement was found to be possible with parenteral ad ministration of as little as 25 μg For example a man 65 with typical pernicious anemia in relapse received two intra muscular injections of 12 5 μg vitamin B_1 each one month apart with subsequent remission of hematologic and neuro logic manifestations There was no evidence of relapse two months later when additional therapy was given A woman 56 with similar evidence of pernicious anemia was given a single intramuscular injection of 25 μg with subjective im provement in gait and paresthesias within 48 hours Six weeks later gait was entirely normal and position sense was intact

The effective oral dose of vitamin B_1 appears to be 40 150 times the minimal parenteral dose although addition of nor mal gastric juice appreciably decreases the amount necessary for therapeutic effect Three patients with pernicious anemia in relapse were each given a single oral dose In one 5 000 μg produced prompt clinical improvement hematologic response was more rapid than had previously been observed after in tensive parenteral liver therapy The second patient given 2 000 μg also showed clinical and hematologic response However three weeks after therapy the hematocrit appeared to reach a plateau at 31 per cent The third who received

(4) J Lab & Cl M d. 38 84 94 J ly 1951

Although the first preparations could substitute for vitamin B_1 as a growth factor for Lactobacillus leichmannii 313 it had no antipernicious anemia action The authors assume that the red pigments are peptide conjugates of vitamin B_{12} which can be utilized for growth of certain lactic acid bacteria but not in the intermediate metabolism of patients with pernicious anemia This assumption is supported by the facts that after treatment with potassium cyanide (1) the red pigments become soluble in butanol and then yield the typical absorption spectra of vitamin B_{12} and (2) the red pigments develop hemopoietic activity, as was shown in three cases (Fig 57) Treatment with potassium cyanide seems to release vitamin B_{12} from peptide linkage it remains to be discovered whether this release by the gastric or duodenal juice of patients with pernicious anemia is insufficient By microbiologic assays alone hemopoietically active vitamin B_{12} cannot be differentiated from less potent peptide conjugates

Preparation of Hemopoietically Active Extracts from Feces Sheila T E Callender and G H Spray[3] (Radcliffe Infirm Oxford) repeated their work on an untreated patient with pernicious anemia of two years ago on a normal person and two more patients with untreated pernicious anemia After being homogenized with water the feces were heated to 90 C cooled and further treated as in the preparation of modern purified liver extracts for parenteral use The final solution was sterilized by filtration through sintered glass

Microbiologic assay of the solution revealed an average B_{12} output daily of about 8 μg from the normal subject and 19 3 8 and 22 μg (mean 15 μg) from the three anemia patients The extracts presumably did not contain enough folic or folinic acid to produce hemopoietic response the largest amount given any of the four patients with pernicious anemia being 38 μg on one occasion Intramuscular injections of the material sometimes caused local tenderness and pyrexia but no more severe or lasting toxic effects In each patient a response appeared similar to that with vitamin B_{12}

[This work like that of Bethell demonstrates the paradox that the feces of the patient with pernicious anemia as well as those of the normal subject contain therapeutically effective amounts of vitamin B_{12} However as it is presumably largely formed in the colon by bacterial

(3) Lancet 1 1391 139 June 1951

patients with pernicious anemia and normal persons than was anticipated

Argentaffin Cells and Pernicious Anemia have been related by Eros and Jacobson Eros claimed evidence of atrophy of the intestinal argentaffin system in patients dying of pernicious anemia and hypothesized that argentaffin cells in the gastrointestinal tract and similar cells in other organs are significant in hemopoiesis Since others disagree with this distribution and relationship Erik Landboe Christensen[5] (Univ of Copenhagen) made histologic studies of freshly fixed specimens of fundus pylorus and duodenum from 50 human beings and 21 hogs using the Masson Hamperl technic whereby

OCCURRENCE OF HEMOPOIETIC ACTIVITY AND ARGENTAFFIN CELLS IN FUNDUS PYLORUS AND DUODENUM OF MAN AND HOG

	O u po M	Ac H m H g	A G M	N H g
Fundus	++	—	(+)	+
Pylorus	+	++	(+)	+
Duodenum	+	++	++	++

substances within specific cells reduce the ammoniacal silver hydroxide without addition of any reducing agent He found that in man argentaffin cells attain their highest development in the duodenum where they are most numerous largest and of the general intestinal type They are fewer in Brunner s glands Pyloric and fundic argentaffin elements do not resemble intestinal elements and are more scattered In the hog as in man duodenal argentaffin cells are well developed and intestinal in type but they are also well developed though less numerous in the pylorus In the fundus though more scattered they are found in every section and are morphologically somewhat different

Clinicotherapeutic investigations have shown a pronounced antipernicious anemia effect of the desiccated and defatted human fundus whereas all attempts to demonstrate such effect of the hog fundus have failed The pronounced effect of the human fundus is not associated with any marked predominance of argentaffin cells in this portion of the stomach (table) These observations do not show parallelism in distribution of argentaffin cells and in localization of the principle

(5) Am J M S 3 18 390 F bru y 195

1 000 μg also improved but to a lesser extent Since about 25 μg vitamin B_1 given parenterally can produce complete re mission it is probable that the patient receiving 5 000 μg orally absorbed 25 μg or more of the ingested vitamin

Two normal adults and two patients with pernicious anemia in remission were given 1 000 μg vitamin B_1 intravenously Two other normal subjects received 25 μg intravenously Plasma from the controls and from patients with pernicious anemia showed vitamin B_{12} activity below 3 5 $m\mu g$/ml This was greatly increased after injection of 1 000 μg Six hours later increased activity was no longer demonstrable Urine obtained before injection of vitamin B_{12} showed no measur able activity after injection about 100 per cent of the vitamin could be accounted for in the urine within eight hours This suggests that excretion of the vitamin is rapid and approxi mately quantitative after parenteral administration of large amounts There was no detectable difference between controls and patients with pernicious anemia After intravenous injec tion of 25 μg urine excreted in the first four hours showed increased B_{12} activity but accounted for less than 15 per cent of the injected material

Urinary response to widely varying amounts of vitamin B_1 administered intramuscularly was studied in 11 controls and 5 patients with untreated and treated pernicious anemia maintained on a vitamin B_{12} deficient diet for at least 24 hours Intramuscular injection of 25 μg or less produced no significant increase in activity of the urine Activity in the first eight hours after injection of 100 μg was greatly in creased accounting for 19 49 per cent of the injected vitamin With a dosage of 500 μg urinary activity in the first eight hours ranged from 86 to 125 per cent of the injected material Again no difference was noted between controls and per nicious anemia patients After oral administration of the vitamin in amounts up to 10 000 μg/dose there was no de tectable increase in B_1 activity of the urine although three patients with pernicious anemia in relapse showed prompt hematologic response

Apparently the body needs only a small amount of vita min B_{12} and normally can absorb this amount from the in testinal tract There is less difference in absorption between

not constant was significant Crystalline vitamin B_{12} appears to represent Castle s extrinsic factor

The table indicates that gastric and serum hemopoietic factors are identical biologically Both are thermolabile and heating results in diminution of megaloblastic ripening in tissue culture but increase in free vitamin B_1 is shown by microbiologic assay These results suggest that Castle s theory that intrinsic factor plus extrinsic factor equals hemopoietic factor is valid However since crystalline vitamin B_{12} given parenterally to pernicious anemia patients appears in serum as the active hemopoietic factor rather than as free vitamin B_1 the intrinsic factor deficiency must be only in the gastric juice and there must be an extragastric source of intrinsic factor with which the parenteral vitamin B_1 can combine This extragastric intrinsic factor cannot be present in a free state since vitamin B_1 added to pernicious anemia serum has no megaloblast ripening effect in vitro

[These results indicating that vitamin B_{12} cannot act independently upon bone marrow cells in vitro are in contrast to those reported by Horrigan *et al* with vitamin B_{12} instilled directly into the marrow cavity in pernicious anemia (see the 1951 YEAR BOOK p 300) Horrigan s report has now been confirmed by others —Ed]

Relation of Glandular Mucoprotein from Human Gastric Juice to Castle s Intrinsic Antianemic Factor The extrinsic food factor and the hemopoietic principle of liver are probably identical with vitamin B_{12} The chief role of the intrinsic factor appears to be that of promoting intestinal assimilation of this vitamin George B Jerzy Glass Linn J Boyd Michael A Rubinstein and Chester S Svigals[7] (New York Med College) believe that in man the main carrier of the intrinsic factor activity of gastric juice is the glandular mucoprotein fraction of the gastric dissolved mucin Both substances are nondializable compounds containing a protein moiety with similar behavior on filtration treatment with alcohol acetone and trichloracetic acid Both are soluble in acid juice are rather resistant to acid peptic digestion and can be stored for an indefinite period in acid gastric juice Like intrinsic factor glandular mucoprotein occurs in the gastric juice of all normal human beings and is not necessarily absent from the gastric secretion in achlorhydria The fundal area from which glandular mucoprotein is derived undergoes the most

(7) S 115 101 108 F b 1 195

active against pernicious anemia nor do they support the assumption that these cells are significant in hemopoiesis

On Nature of Castle's Hemopoietic Factor Although the validity of Castle's observations on the relation of achylia gastrica to pernicious anemia has never been doubted folic acid seems to have no place in the classic scheme and vitamin B_{12} has features common to both extrinsic and hemopoietic factors Sheila T Callender and L G Lajtha[6] (Radcliffe Infirm Oxford) used marrow cultures to investigate further the relation between vitamin B_{12} and the hemopoietic factor in normal serum

METHOD—Marrow cell suspensions from untreated patients with pernicious anemia were cultured and differential counts made on

RELATION BETWEEN GASTRIC AND SERUM HEMOPOIETIC FACTOR

TEST SUBSTANCE	MICROBIOLOGIC ACTIVITY	EFFECT ON MEGALOBLASTS IN VITRO
B_{12} crystalline	+	—
Heated	+	—
B_{12} + intrinsic factor	—	+
Heated	+	—
Normal serum	(+)	+
Heated	+	(+)
Treated PA serum	(+)	+
Heated	+	

the nucleated red cells after 48 hours The following were tested for their effect on megaloblasts cultured in 80% pernicious anemia serum plus 20% Ringer's solution (1) gastric juice alone (IF) (2) gastric juice plus B_{12} (HPF) (3) heated gastric juice plus B_{12} (heated IF plus B_{12}) (4) gastric juice plus B_{12} heated (heated HPF) Megaloblastic marrows were also cultured in parallel in 80% (1) fresh normal serum and (2) the same serum previously heated to 56 57 C for 1½ 2 hours

It was found that normal gastric juice (IF) and B_{12} separately were inactive but together (HPF) they produced significant ripening of megaloblasts in vitro Incubation of the mixture before addition to the cultures was unnecessary No ripening effect occurred with heated gastric juice plus vitamin B_1 Results with gastric juice plus B_{12} heated suggest partial destruction of HPF with boiling for 5 minutes and more complete destruction with autoclaving Some normal serums heated to 56 C for 1½ 2 hours tend to show less ripening effect than the same serums unheated which though

(6) Blood 6 1234 1239 Dec 1951

refractory achlorhydria and premature graying hair were lacking

Anemia was macrocytic with high color index and in creased corpuscular volume except in the toddler period when iron deficiency is common Smears showed pronounced aniso cytosis and poikilocytosis and occasional basophilic stippling and circulating megaloblasts Leukopenia and decidedly re duced reticulocytes were also noted Marrow was identical with that of pernicious anemia and after liver or vitamin B_1 therapy became normoblastic with increasing reticulocytes red cells hemoglobin content and white cells

None of the children gave evidence of sprue celiac dis ease parasitic infestation or dietary deficiency Response to and repeated relapse after B_{12} therapy and failure in one patient to respond to folic acid eliminated infantile megalo blastic anemia No history of anemia was found in either family One patient had a mild relapse followed in a few weeks by spontaneous remission with no subsequent relapse for five months Long failure to diagnose the disease in this patient was attributed to transfusions which induced temporary remissions As in true pernicious anemia many relapses in these patients followed acute infections

Three of the four patients had glossitis which responded promptly to specific treatment it was not invariably associ ated with each relapse During relapse one patient had transitory minor neurologic changes which promptly cleared on treatment but her sister had none The other pair of siblings had severe neurologic disturbances with pyramidal tract involvement and ataxic gait the older child had diffuse central nervous system involvement during the severe re lapse Both responded to liver and vitamin B_1 but the condition of one was clearly aggravated by folic acid both had residual neurologic damage

Free hydrochloric acid was noted in three of the four after and often without histamine Achlorhydria to hista mine was noted only in relapse in one but became permanent later in two others suggesting that atrophy of gastric mucosa and achlorhydria may be the result rather than cause of lack of intrinsic factor [More likely differential loss of secretory capacity —Ed]

severe atrophy in pernicious anemia This mucoprotein is absent from the juice of patients with pernicious anemia and is present in the gastric juice of patients with other types of anemia

Nine patients with proved pernicious anemia (untreated or in relapse) were given vitamin B_{12} orally alone then the same dose of vitamin B_1 together with gastric mucoprotein and finally vitamin B_{12} alone parenterally The patients re also studied during control periods when no medication was given periodically, blood cell and reticulocyte counts hematocrit determinations and bone marrow studies (iliac crest) were done In two patients oral treatment with vitamin B_{12} and mucoprotein was not adequate to prevent relapse It was discovered that the relation between the factors was not stoichiometric With a daily dose of 30 μg vitamin B_1 50-75 mg glandular mucoprotein usually sufficed if given daily for 10 days to obtain an optimal hemopoietic response But with the dose of 10 20 μg vitamin B_1 even 100 mg mucoprotein/day was usually insufficient and the response was obtained only when this amount of vitamin B_1 was combined with a daily dose of 150 200 mg glandular mucoprotein In itself administration of mucoprotein causes no hemopoietic activity in pernicious anemia

Despite detailed biochemical study it cannot yet be stated if glandular mucoprotein is the pure intrinsic factor or whether the intrinsic factor is contained or adsorbed on its molecule

[Identity with intrinsic factor would seem unlikely since 0 6 mg daily of a relatively simple fraction of gastric juice has been shown to potentiate markedly the activity of 5 μg vitamin B —Ed]

Juvenile Pernicious Anemia Peak incidence of this disease which results from failure to absorb vitamin B_1 because of lack of intrinsic factor in gastric juice is in the sixth decade and it has seldom been described in childhood Edward H Reisner Jr James A Wolff R James McKay Jr and Eugenia F Doyle[8] (New York City) review 175 probable cases from the literature and describe two pairs of siblings believed to have true addisonian pernicious anemia first noted at 2 and 8 years and 4 and 22 months respectively Of the features common in this disease only persistent histamine

(8) P d t c 8 88 106 July 1951

mortality in the present group was compared with that in the average population Among females death rate was only 13% higher than the average whereas in males it was more than double that of the average male population this is hardly coincidental Death rate was most striking in the youngest group and in the first years of the follow up

No difference between male and female was found in age distribution severity of anemia on hospitalization or nature and number of coexistent diseases at beginning of observation As for cause of death gastric carcinoma showed decided predominance in males especially in the youngest group (five of six) Even without deaths from gastric carcinoma a considerable excess of mortality in males over females re mained To see if the anemia might have caused the differ ence the red blood picture shortly before death for males and females was examined No difference was found in mean values

When grouping red blood cell and hemoglobin levels ac cording to age after start of observation period the average values for males who lived the shortest time were lowest whereas those for males who lived longest were highest (red blood cell 2 84 vs 4 37 and hemoglobin concentration 60 vs 95%) This difference did not appear in the histories of females Similar age grouping at start of follow up showed no distinct difference but if males were similarly grouped within individual age groups the correlation reappeared re gardless of how few were considered

Further comparison showed that males with low blood values at death survived a shorter average time after coming under observation than those with high values at death This was also not found among the females It is suggested that males have less tolerance for inadequately treated anemia than females perhaps because the female unlike the male is better equipped to meet blood loss because of physio logic loss due to menstruation and parturition Similar results have been found in other diseases e g arterial hypertension which is better tolerated by females than males

[In our exper ence with patients g ven at least 15 U S P units of purified liver extract or 15 µg vitamin B_{12} by i tramuscular injection at four week intervals the development of any symptoms or s gn includ g anem a indicates a complicat on not recrudescence of pernicious anemia —Ed]

All four responded to vitamin B_{12} given parenterally but three did not when it was given orally in 5 μg daily doses two siblings responded promptly when 5 μg vitamin B_{12} was given daily with 350 cc normal gastric juice All this evidence points to the conclusion that the anemia was caused by failure to absorb vitamin B_{12} because intrinsic factor was lacking in the gastric juice and therefore represents true pernicious anemia

[These patients are to be distinguished from infants with megaloblastic anemia due to folic acid rather than vitamin B_{12} deficiency described in the preceding article —Ed]

Mortality Among Patients with Pernicious Anemia in Denmark and Incidence of Gastric Carcinoma among Same Jorgen Jorgensen[9] (University Hosp , Copenhagen) reviews a series seen during 1930-42 For purposes of selection pernicious anemia was diagnosed (1) when there were typical reticulocytosis and increase in red blood cells after administration of liver or stomach preparations and (2) o contradictory data Of 208 patients (58 male) meeting these criteria and followed up during 1944-47 80 had died Average follo up period was 7 8 years Nearly all survivors had continued treatment but often it was not enough to maintain a normal blood picture

Gastric carcinoma was listed as cause of 12 of the 80 deaths 11 were verified by case record No tumor was operable at the time of diagnosis Comparison of actual deaths from gastric carcinoma with the average expected deaths from carcinoma in a group of similar size and composition among the Danish population showed combined mortality three times that expected Six of the 58 male patients died of carcinoma as against calculated incidence of 0 7 among the females six of 148 died as against 2 9 calculated Although the totals were small the preponderance for males was striking

Since all thorough studies of this problem have shown a similar trend incidence of gastric carcinoma is definitely higher in pernicious anemia patients than in the population as a whole Among patients in this series dying of gastric carcinoma males were younger on the average than females (one of six males over 63 one of six females under 72)

To check the effect of pernicious anemia on mortality

(9) ct m d a d n v 139 471 481 1951

of these cells from their precursors or granulocytic hyper plasia can block the marrow

Side Effects of Preparation of Vitamin B_1 Although it was effective and inexpensive P D Bedford (Oxford) found a vitamin B_{12} concentrate derived from Streptomyces griseus fermentation liquors (solution A) to cause several undesirable side effects These consisted when moderately severe of pain and tenderness at the site of injection with fever shivering and malaise beginning 6 hours after the injection and lasting 24 hours To determine their cause intradermal skin tests were performed on 100 people Control substances were a vitamin B_{12} concentrate prepared from liver (solution B) and a purified (by crystallization) form of the test concentrate (solution C) Fifty two subjects had received one or more antibiotics within the previous five years Of these 10 (19%) were skin positive to A whereas this was true of only 4 (8%) of the persons who had not previously received antibiotics These 14 subjects were then given intra muscular injections of each solution as were 14 A negative controls No subject reacted adversely to solution B or C but six did to solution A Of these four were in the skin positive group and five were persons who had previously received antibiotics

Results indicated that the factor responsible for the sen sitivity reactions and side effects was an impurity present in solution A absent in B and present in traces in C It was probably carried over from the culture broth People who have previously received penicillin or other antibiotics are over twice as likely to react to these mold impurities as are those who have not been so treated The possibility of inducing idiosyncrasy to antibiotics argues against use of impure preparations of vitamin B_{12} derived from mold cultures

Development of Neurologic Manifestation of Pernicious Anemia during Multivitamin Therapy in 5 of 10 patients seen during 1950 is reported by C Lockard Conley and Julius R Krevans[3] (Johns Hopkins Univ) Because these patients had little anemia diagnosis was not always readily apparent and some were first thought to have multiple sclerosis or

(2) B t M J 1 690 691 M 9 1952
(3) N w E gl d J Med 245 5 9 531 Oct 4 1951

Leukemoid Bone Marrow in Pernicious Anemia Maurice B Strauss Radford Brokaw (V A Hosp Framingham Mass) and Carleton B Chapman[1] (V A Hosp Minneapolis) made this observation in two patients in relapse complicated by infection Despite leukopenia of the peripheral blood marrow specimens showed intense myelocytic activity with insignificant numbers of megaloblasts (Fig 58) In both cases



Fig 58—Marrow in pernicious anemia ... granulocytic series ... (Courtesy of ... M B et al Am J M Sc 223 54 60 January 1952)

diagnosis of aleukemic leukemia was seriously entertained The patients responded to vitamin B_{12} and subsequent study showed entirely normal marrow It was concluded that the marrow in pernicious anemia in relapse is not always pathognomonic

Infection may have served as stimulus for the extensive myelocytic proliferation in the marrow Possibly because of absence of a necessary maturation factor these cells failed to develop into adult leukocytes Why megaloblasts were so sparse is not clear Either infection can inhibit development

(1) Am J M Sc 223 54 60 January 1952

liver extract in dosage of 15 30 units a week and 15 units every two weeks respectively had an arrest of neurologic disease when the dose was increased to 75 units a week and 45 units every two weeks One patient who had an arrest when liver extract therapy was instituted improved more rapidly when folic acid was stopped In the two remaining patients who had abnormal nutrition and complicating organic ab normalities nervous system disease progressed on combined therapy There was gradual improvement when folic acid was omitted Neurologic disease did not develop in 6 per nicious anemia patients treated with folic acid and liver extract therapy for 3½ 39 months nor in 14 patients maintained on liver extract or vitamin B_1 alone for 4 39 months after omission of folic acid Five of the latter in whom progressive neurologic disease developed after folic acid therapy showed definite improvement when placed on liver extract or vitamin B_1 Combined therapy for as long as 38 months produced the same hematologic levels as either folic acid or liver ex tract alone

Folic acid alone for 3 25 months did not produce neuro logic disease in patients with iron deficiency anemia who had free hydrochloric acid in the gastric secretions and pre sumably sufficient intrinsic factor It did not influence response to ferrous sulfate therapy In one patient with a total gas trectomy and mild macrocytic anemia subacute combined de generation developed after five months of folic acid therapy One patient with nontropical sprue had an exacerbation of paresthesias of the fingers while receiving 15 mg folic acid daily for two months this later proved unrelated to folic acid therapy It is suggested however that patients with sprue nutritional macrocytic anemia and other macrocytic anemias associated with gastrointestinal tract pathology who are treated with folic acid should receive supplemental liver ex tract or vitamin B_{12} to insure against development of nervous system disease

These observations are explained by the theory that the hematologic and neurologic manifestations of pernicious anemia and other macrocytic anemias associated with gastro intestinal tract pathology and inadequate nutrition are due to deficiency of more than one substance Administration of folic acid may improve the hematologic status but induce a de

other neurologic disorders Although none was aware of taking folic acid each had been using multivitamin preparations At least four of the five preparations used contained enough folic acid to produce hematologic remission

Early symptoms of pernicious anemia include weakness vague gastrointestinal disturbances unimpressive paresthesias and sore tongue for which patients often receive vitamins A survey of proprietary vitamin mixtures as of January 1951 revealed that over 80 contained folic acid providing 0 2-48 mg folic acid daily Most of them provided more than 5 mg folic acid daily which will maintain prolonged hematologic remission in pernicious anemia patients

Such combinations may permit development of progressive severe subacute combined degeneration while the blood picture remains normal Thus any patient having sore or burning tongue should be carefully examined to exclude pernicious anemia before multivitamins are prescribed Neurologic abnormalities resembling combined system disease should always be attributed to pernicious anemia until proved otherwise Histamine achlorhydria in a patient with this disorder indicates intensive parenteral vitamin B_{12} treatment even when blood and bone marrow are normal Good clinical response to such therapy strongly supports diagnosis of pernicious anemia

Incorporation of vitamin B_1 in multivitamin preparations does not protect the patient with pernicious anemia against the development of subacute combined degeneration Vitamin B_1 is poorly absorbed in this disease and must be given parenterally for optimal effect

Effects of Combined Folic Acid and Liver Extract Therapy Folic acid administered alone induced hematologic remission but did not prevent development or progression of subacute combined degeneration in 12 of 22 pernicious anemia patients receiving this agent for 12 25 months Robert B Chodos and Joseph F Ross[4] (Boston) then investigated the effect of combined liver extract and folic acid on these patients In 10 with good nutrition neurologic relapses did not progress with combined therapy including usually from 5 to 30 mg folic acid per day Two patients who had initial progression of subacute combined degeneration while receiving

(4) Blood 6 1 13 123 D ember 1951

liver extract in dosage of 15 30 units a week and 15 units every two weeks respectively had an arrest of neurologic disease when the dose was increased to 75 units a week and 45 units every two weeks One patient who had an arrest when liver extract therapy was instituted improved more rapidly when folic acid was stopped In the two remaining patients who had abnormal nutrition and complicating organic ab normalities nervous system disease progressed on combined therapy There was gradual improvement when folic acid was omitted Neurologic disease did not develop in 6 per nicious anemia patients treated with folic acid and liver extract therapy for 3½ 39 months nor in 14 patients maintained on liver extract or vitamin B_{12} alone for 4-39 months after omission of folic acid Five of the latter in whom progressive neurologic disease developed after folic acid therapy showed definite improvement when placed on liver extract or vitamin B_1 Combined therapy for as long as 38 months produced the same hematologic levels as either folic acid or liver ex tract alone

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ficiency of another substance or substances e g vitamin B_{12} *which are essential for maintenance of a normal blood picture* and the integrity of the central nervous system This deficiency will eventually result in development of a suboptimal blood picture or subacute combined degeneration of the spinal cord or both

[This article shows that when vitamin B_{12} is given *by injection* and is therefore available to metabolic processes in the body folic acid has *no deleterious effect on the nervous system Our experience fully* confirms this —Ed]

Vitamin B_{12} in Megaloblastic Anemia of Pregnancy and Tropical Nutritional Macrocytic Anemia has heretofore produced contradictory results S *Chaudhuri*[5] (Lady Hardinge Med College New Delhi India) reports 21 cases of megaloblastic anemia in women treated with vitamin B_{12} All were hospitalized and given *no other treatment* Bone marrow was megaloblastic in all cases Most patients were severely anemic *having had no previous treatment Vitamin* B_{12} *was given* intramuscularly in 20 μg doses either every other day or every fifth day depending on the patient s condition

Patients were aged 19-45 years with only 6 past 30 Five were treated in the third trimester of pregnancy and 11 within *three months after delivery The other five had history of* frequent diarrhea and poor nutrition Nine had macrocytic hypochromic and 11 macrocytic normochromic anemia Initial red cell count was below 1 000 000 in 4 below 1 500 000 in 11 below 2 000 000 in 2 and below 2 500 000 in 4 Total protein levels especially of albumin were low in all cases and were associated with dependent edema in 15 Reticulocyte values *after treatment varied between 3 5 and 25% with maximum* usually on the 7 10th day

Response to vitamin B_{12} was adequate in 20 One responded better when iron was added during the third week Another with sore tongue and diarrhea had a poor hematologic though good clinical response but later improved rapidly on folic acid given parenterally The minimal amount of vitamin B_{12} used was 60 μg in 15 days and the maximal 360 μg in 53 days Roughly in mild cases an average of 4 μg a day was needed to produce improvement and in severe cases as much as 10 μg a day It was also found that anemia with pregnancy required higher doses

(5) B M J 858 Oct 6 1951

The suggestion that vitamin B_{12} could not be effective in macrocytic anemia in the tropics resulted from a long standing concept that refined liver had little effect This was disproved by Patel and Bhende In their report the requirement in tropical macrocytic anemia was two or three times that in addisonian pernicious anemia The same requirement was shown for vitamin B_{12} The present investigation also shows that vitamin B_{12} is effective but that higher doses are required than in pernicious anemia

[This conclusion though probable is not established by demonstration of *failure* of usual effective doses of vitamin B_{12} e g 1 μg a day intra muscularly Indeed one patient who received only 2 μg daily displayed a reticulocyte peak of 13 5% on the sixth day from an initial red cell level of 2 000 000 and during 30 days averaged a rise of 580 000 red cells per week!—Ed]

Experimental Nutritional Megaloblastic Anemia Relation of Ascorbic Acid and Pteroylglutamic Acid I Nutritional Data and Manifestations of Animals As early as 1932 megalo blastic anemia was developed by dietary means alone in monkeys which responded to a factor later identified as pteroylglutamic acid Since a single treatment with it pro duces lasting cure of megaloblastic anemia in infancy it seemed that some dietary feature might permit deficiency of this substance This anemia usually occurs in early infancy when diets are principally milk Also these infants [and formerly some proprietary baby foods—Ed] are deficient in ascorbic acid To check this thesis Charles D May R D Sundberg Frances Schaar C U Lowe and R J Salmon[6] studied young monkeys consuming milk diets severely de ficient in ascorbic acid and low in folic acid

The animals gained weight and showed no ill health for 6-12 weeks after which varying but progressive anorexia weight loss and the first clinical signs of scurvy developed With appearance of scurvy confirmed by periorbital hemor rhages weight loss and anorexia rapidly caused pronounced emaciation No evidence of respiratory infection was noted in any Generally diarrhea developed with scurvy sometimes so severe and dehydrating that parenteral fluids were needed The authors do not consider this causally related to scurvy or anemia however since megaloblastic anemia developed in the same period in some animals which had no diarrhea and

(6) A M A Am J D Child 8 82 309 September 1951

because it did not respond to antibiotics but ceased when effective vitamin therapy was begun

Every animal not given ascorbic acid regularly or recently developed anemia with megaloblastic marrow within one month after scurvy appeared With respect to production of anemia or megaloblastic marrow changes no significant differences were noted among the various types of milks soy bean formula protein content of diets or with decrease in food intake These changes were virtually indistinguishable from those of pernicious and other megaloblastic anemias in man Marrow was hyperplastic the dominant cells being developing erythrocytes Developing neutrophils showed striking increase in size premature segmentation and hyperlobulation Interpretation of peripheral blood changes was difficult because normal control monkeys had microcytic slightly hypochromic erythrocytes with reference to normal human red cells Leukopenia was common but not constant Of primary importance was the fact that blood pictures comparable to those in megaloblastic anemias of man had been found in megaloblastic monkeys

Vitamin B_1 had no effect on marrow blood or clinical signs therapeutically or as supplement In sharp contrast folic acid orally or intramuscularly caused prompt disappearance of the megaloblastic pattern in the marrow improvement in appetite and relief from diarrhea without ascorbic acid Without ascorbic acid however the animal later died of scurvy Anemia with normoblastic marrow developed after scurvy after treatment with pteroylglutamic acid and even with vitamin B_1 This anemia was believed due to iron deficiency from the hemorrhages characteristic of scurvy

Previously a folic acid conjugate was also found effective even when given orally without ascorbic acid Deficiency of ascorbic acid apparently leads to deficiency of or disturbance in metabolism of folic acid Megaloblastosis can be prevented or eliminated without ascorbic acid if sufficient pteroylglutamic acid is given Megaloblastic anemia could also be eliminated and the animal restored to normal with ascorbic acid alone while the experimental diet was continued Presumably ascorbic acid is effective because it allows reaccumulation of pteroylglutamic acid or restores its metabolism to normal Ascorbic acid enhances production of f ic acid

(citrovorum factor) from pteroylglutamic acid and effects of varying doses of ascorbic and folic acids and citrovorum factor in these animals are compatible with this theory in vivo Daily injection of 7 5 μg folinic acid was as effective as 750 μg folic acid in different animals It was incidentally noted that aureomycin given for diarrhea did not affect the megaloblastic marrow pattern

[These experiments probably indicate the dual deficiency basis of at least some megaloblastic anemias of infants folic acid and vitamin C See following article —Ed]

Citrovorum Factor and Folic Acid in Treatment of Megaloblastic Anemia in Infancy Citrovorum factor a nutrient required by Leuconostoc citrovorum is a metabolite of folic acid and is excreted in the urine of man and rats after administration of folic acid It can reverse the toxic effects of aminopterin and induce hemopoietic response in patients with pernicious anemia Although in vitro synthesis from folic acid and subsequent isolation in crystalline form have been accomplished its structure has not been reported Calvin W Woodruff J Cyril Peterson and William J Darby[7] (Vanderbilt Univ) discuss two infants with megaloblastic anemia who responded to this factor

They were twins aged 10/ months At birth each weighed 3 lb 5 oz They had a fair dietary history and had been hospitalized several times for acute infection Both had received transfusions for moderately severe hypochromic anemia three months before the present hospitalization

Intermittent diarrhea anorexia and poor weight gain preceded admission of the boy Examination showed pallor irritability generalized lymphadenopathy and hepatosplenomegaly Megaloblasts were increased in the sternal marrow With whole milk he was given 500 000 units [equivalent to 75 μg —Ed.] of citrovorum factor intramuscularly daily for 18 days Seventy two hours after the first injection marrow normoblasts were remarkably increased A second course consisting of twice as much citrovorum factor produced no further response and the anemia did not recur subsequently

The girl was ho pitalized when her twin s illness was diagnosed Physical examination revealed only pallor but despite the relatively mild anemia marrow changes were more pronounced She also was fed whole cow s milk alone and given 500 000 units of citrovorum factor intramuscularly daily Hematologic changes are shown in Figure 59 Marrow changes were the same as those in the boy After 13 days of this therapy a single dose of 5 mg folic acid given intramu cularly caused no secondary reticulocytosis After

(7) P oc Soc E p B ol & Med 77 16-18 M y 1951

because it did not respond to antibiotics but ceased when effective vitamin therapy was begun

Every animal not given ascorbic acid regularly or recently developed anemia with megaloblastic marrow within one month after scurvy appeared With respect to production of anemia or megaloblastic marrow changes no significant differences were noted among the various types of milks soy bean formula protein content of diets or with decrease in food intake These changes were virtually indistinguishable from those of pernicious and other megaloblastic anemias in man Marrow was hyperplastic the dominant cells being developing erythrocytes Developing neutrophils showed striking increase in size premature segmentation and hyperlobulation Interpretation of peripheral blood changes was difficult because normal control monkeys had microcytic slightly hypochromic erythrocytes with reference to normal human red cells Leukopenia was common but not constant Of primary important was the fact that blood pictures comparable to those in megaloblastic anemias of man had been found in megaloblastic monkeys

Vitamin B_{12} had no effect on marrow blood or clinical signs therapeutically or as supplement In sharp contrast folic acid orally or intramuscularly caused prompt disappearance of the megaloblastic pattern in the marrow improvement in appetite and relief from diarrhea without ascorbic acid Without ascorbic acid however the animal later died of scurvy Anemia with normoblastic marrow developed after scurvy after treatment with pteroylglutamic acid and even with vitamin B_1 This anemia was believed due to iron deficiency from the hemorrhages characteristic of scurvy

Previously a folic acid conjugate was also found effective even when given orally without ascorbic acid Deficiency of ascorbic acid apparently leads to deficiency of or disturbance in metabolism of folic acid Megaloblastosis can be prevented or eliminated without ascorbic acid if sufficient pteroylglutamic acid is given Megaloblastic anemia could also be eliminated and the animal restored to normal with ascorbic acid alone while the experimental diet was continued Presumably ascorbic acid is effective because it allows reaccumulation of pteroylglutamic acid or restores its metabolism to normal Ascorbic acid enhances production of folinic acid

counts to normal were not possible in most instances Dosage of leucovorin ranged from 3 to 12 mg daily

In one patient with megaloblastic anemia of pregnancy vitamin B_{12} (80 μg intramuscularly) had produced a moderate reticulocyte response but no change in the marrow picture (red cell count had actually dropped by the 12th day) Response to leucovorin intramuscularly (12 mg daily at first gradually decreased to 3 mg daily) caused a good reticulocyte response and an increase in red blood cells from 1 560 000 to 4 060 000/cu mm in 27 days The other patient with megaloblastic anemia of pregnancy showed similar good response in reticulocyte count change in the marrow picture and increased red cell count

The patient (aged 67) with idiopathic steatorrhea had a four year history of diarrhea and anorexia with a weight loss of 28 lb Absorption of fat was only 66 6% (normal 90 95%) Leucovorin 9 mg intramuscularly daily for four days caused immediate hematologic response reticulocyte count increasing and bone marrow appearing normoblastic After 4 days pteroylglutamic acid (10 mg twice daily for 66 days) was begun red cell count and hemoglobin content rose to essentially normal values the number of stools decreased and appetite improved

Intestinal Macrocytic Anemia has been reported in association with intestinal strictures and anastomoses especially after repair of a gastrojejunocolic fistula or a stagnant intestinal loop Sixty cases have been collected In 37 patients one or more strictures were present whereas 23 had anastomoses Only six strictures involved the colon Of the anastomoses 14 were enteroenterostomies or enterocolostomies and 9 were gastrocolic or high jejunocolic fistulas Fewer cases are being seen because of the decline in incidence of intestinal tuberculosis which has been the prime cause of stenosis and because of avoidance in recent surgery of formation of stagnant loops of intestine In anemia associated with these lesions the basic abnormality seems to be a stagnant or obstructed portion of small intestine and infection of the stomach and small intestine with colonic organisms Clinically patients may present a sore tongue Free acid is present in the gastric juice of over half the patients Steatorrhea is not necessarily

discharge she continued to thrive Minimal effective parenteral dose of citrovorum factor was thus assumed to be less than 5 μg daily

The first of two other infants with megaloblastic anemia failed to respond to 30 μg vitamin B_{12} given parenterally Reticulocytosis increase in red cell count and hemoglobin concentration and reversion of marrow to normal followed

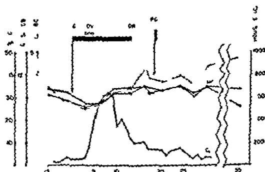


Fig 59—Response of megaloblastic anemia of infancy to citrovorum factor Failure to obtain additional response to folic acid (Courtesy of Woodruff C W et al Proc Soc Exper Biol & Med 77 16 18 May 1951)

500 μg folic acid a day orally The other patient responded similarly to 200 μg of folic acid given orally daily

Since the daily requirement of citrovorum factor parenterally is less than 75 μg and of folic acid orally less than 200 μg it cannot be decided which is the more active

[In pernicious anemia moderate hemopoietic responses in two of four of our patients have followed the daily intramuscular injection of 25 μg folic acid —Ed]

Treatment of Megaloblastic Anemias with Citrovorum Factor is reported by L S P Davidson and R H Girdwood[8] (Univ of Edinburgh) Of nine women studied six with addisonian pernicious anemia responded satisfactorily to intramuscular or oral treatment with the citrovorum factor one with idiopathic steatorrhea responded poorly to this treatment and two with megaloblastic anemia of pregnancy responded extremely well to intramuscular or oral administration of the factor (leucovorin)

Initially all showed hematologic improvement However for lack of sufficient drug supplies attempts to restore blood

(8) Lancet 2 1193 1195 Dec 24 1951

1 300 000 and hemoglobin value 3 5 Gm /100 cc and was given 400 000 units daily for 17 days Dramatic improvement in sense of well being and especially of appetite was noted within 24 hours Gastric analysis after histamine injection was normal A maximal reticulocyte response of 26% was noted in five to eight days At 15 days the expected red cell count and hemoglobin level were reached In both patients over all response was similar to that obtained with crude or refined liver extract vitamin B_{1} or folic acid Marrow reverted to normal megaloblasts disappearing rapidly and giant stab cells more slowly

The response to penicillin which contains no vitamin B_{1} may be due to any or all of the following factors (1) changes in intestinal flora which may lead to destruction of antagonists or competitors or other factors which may be interfering with synthesis absorption or utilization of hemopoietic factors (2) interference with bacterial metabolism thus releasing hemopoietic factors for the body s use (3) an effect on protein metabolism and synthesis of nucleoproteins from basic amino acids (4) presence of hitherto unknown hemopoietic factors and (5) destruction of toxins produced by bacteria It seems that in pregnancy the extra drain on the hemopoietic system necessitates continuation of treatment or perhaps higher doses

[The case report includes no temperature record or other evidence pro or con the presence of complicating infection The usual antibacterial effect of penicillin is the most probable explanation of the sudden improvement within 24 hours Infection is well known to inhibit erythropoiesis —Ed]

HYPOCHROMIC ANEMIAS

Studies on Iron Deficiency Anemia of Pregnancy Including Plasma Volume Total Hemoglobin Erythrocyte Protoporphyrin in Treated and Untreated Normal and Anemic Patients Curtis J Lund (Louisiana State Univ) carried out these studies to show how determinations of plasma volume and erythrocyte protoporphyrin augment routine hematologic methods in identification of iron deficiency and evaluation of response to therapy Except for screening tests all blood was drawn by venipuncture heparin being used as an anticoagu

(2) Am J Obst & Gyn 62 947 963 November 1951

present Cord changes do occur Bone marrow is megaloblastic the macrocytic anemia responds to liver treatment although at times slowly Surgical correction of the intestinal lesion may permanently cure the anemia

G M Watson and L J Witts[9] (Radcliffe Infirm Oxford) devised a means of producing macrocytic anemia in rats Because earlier operations to produce stricture or obstruction had indicated that in rats in which anemia developed there was always some dilatation of a blind loop they decided to increase filling of the blind loop by dividing the small intestine at the junction of the middle and lower thirds and anastomosing the lower portion to the side of the small intestine at the junction of its upper and middle thirds (i e by reversing direction of peristalsis in the blind loop) Owing chiefly to the high operative mortality final yield of rats with anemia is about 20% It sometimes happens therefore that a fairly large consecutive series is operated on without anemia developing The cases of anemia tend to occur in crops as if some common initiating factor appears periodically The most likely cause of the anemia is an alteration of the intestinal flora analogous to that which occurs in gastrocolic fistula in man and it is possible that the intestinal bacteria are in some way involved with the absorption or utilization of hemopoietic substances The anemia is associated with hemolysis and sometimes with steatorrhea It responds well to folic acid or aureomycin but poorly if at all to vitamin B_{1} The anemia differs from the blood disorder produced in the rat by folic acid deficiency which is macrocytic without hemolytic features and in which leukopenia is more prominent than anemia

[It is not certain that the experimental anemia in rats is analogous to that of the patients The human anemia appears to have responded promptly in some instances to parenteral liver therapy (which probably means to vitamin B) However presence of folic acid especially in early preparations cannot be excluded —Ed]

Response of Megaloblastic Anemia of Pregnancy to Crystalline Penicillin G is discussed by Henry Foy Athena Kondi and Anthony Hargreaves[1] A nonpregnant woman with an apparent case of pernicious anemia was successfully treated with penicillin G (2 800 000 units in seven doses) Therefore the drug was tried in a patient with megaloblastic anemia of pregnancy She appeared gravely ill with red cell count

(9) Brit M J 1 13 17 Jan 5 1952
(1) Ibid pp 1108 1110 May 19 1951

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(2) Am J Ob t & Gy (2 947 963 N mb 1951

lant Hemoglobin was determined photoelectrically as oxy hemoglobin Packed red cell volume was determined by means of the Wintrobe hematocrit Plasma volume was measured in a single venous sample drawn exactly 10 minutes after in jection of T 1824 Free erythrocyte protoporphyrin was de termined on red cells by the Watson Grinstein method

Capillary hemoglobin value of 4 015 patients was deter mined at their first prenatal visit About 20% had levels below 10 Gm /100 cc and 50% below 11 Gm Levels found in finger prick samples were consistently 0 5 Gm lower than those found in samples obtained by venipuncture

Complete studies were done on 66 patients during 402 outpatient examinations Initially there were 31 controls and 35 patients under treatment Five controls later required therapy making a total of 40 treated patients Patients with sickle cell disease Holly s refractory anemia of pregnancy Mediterranean anemia and acute hemolytic anemia were ex cluded Only two patients had megaloblastic anemia of pregnancy

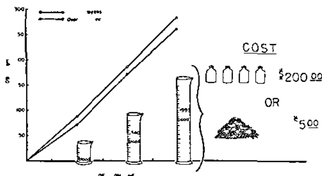
Invariably plasma volume increased during pregnancy Minimum was 14% and maximum 121% (average 48) The peak was usually passed between the 32d and 38th week Changes in plasma volume were generally unrelated to pres ence or absence of anemia

The basic reliability of the packed cell volume test determination of hemoglobin in grams/100 cc blood and red cell count rests on a stable plasma volume When plasma volume is known total hemoglobin equals grams of hemo globin/100 cc blood times total blood volume Total hemo globin mass increases during normal pregnancy becoming demonstrable about the 24th week and reaching a maximum at term with an average increase of 15% It lags behind the rapidly increasing plasma volume

When globin is removed from hemoglobin a heme mole cule remains which consists of iron bound to a porphyrin ring Normally there is little free erythrocyte protoporphyrin most of it being bound with iron The range is usually 20-40 gamma % (maximum 60) In iron deficiency more eryth rocyte protoporphyrin remains free and more is found in the red cells Most patients in this study had some elevation but there was no obvious correlation between [illegible]gree of

anemia and erythrocyte protoporphyrin value Most levels became normal after eight weeks of iron therapy

Fourteen normal patients without iron deficiency served as untreated controls Plasma volume was greatly increased by the 24th week (41%) and reached a peak of 56% by the 36th week One patient had a plasma increase of 93% with hemoglobin value of 9 1 Gm /100 cc but an increase in total hemoglobin mass of 18% During the first two postpartum months total hemoglobin mass dropped an average of 14% (86 Gm or the equivalent of 700 cc whole blood) Yet



F g 60 —T tal h mogl b pon ft on th py Th peut po ot l t d to d t t p g cy If on d fi cy m d co d l t th 34th t 36th w k f g t t n th ll ffi t t m f su f l th py (C rt y f L d C J Am. J Ob t. & Gy 6 947 963 N mbe 1951)

average estimated blood loss postpartum was only 260 cc

Seven patients without evidence of anemia served as treated controls They were on an adequate diet plus supplementary molybdenized ferrous sulfate 6 gr three times a day during the last half of pregnancy Results paralleled those in the normal untreated controls

The anemia controls consisted of 10 patients with micro cytic hypochromic anemia Total hemoglobin value decreased an average of 13% between the 32d and 36th week At this time five patients were so severely anemic that therapy was necessary Erythrocyte protoporphyrin was elevated and con tinued to rise as the anemia progressed reaching an average of 197 gamma % before therapy was given or before delivery

Complete studies were made of 39 patients with anemia

before and during treatment They were divided into two groups those treated before the peak of plasma volume was reached (32 34 weeks) and those treated after that Figure 60 shows the total hemoglobin response of each group in grams and the equivalent in terms of whole blood Iron given orally for six weeks will produce the equivalent of four transfusions in the anemic mother at a fraction (1/40) of the cost If the therapeutic response of the two groups is judged by grams of hemoglobin/100 cc and packed cell volume it seems better to treat the patient late in pregnancy If total hemoglobin mass is used for comparison however rate of response of the two groups is essentially the same Erythrocyte protoporphyrin usually fell within the normal range after six to eight weeks of iron therapy Twenty five of 27 additional patients who were only partly studied responded as well as the others Of a total of 68 patients with iron deficiency anemia 2 (3%) failed to respond to molybdenized ferrous sulfate given orally Of 75 patients given this preparation 1 stopped treatment because of gastrointestinal symptoms There was no evidence that maternal complications were related to presence or degree of anemia though the groups were too small to be of much significance

[The interpretation of plasma volume measurements by the dye method is difficult and that here it measures only the volume of fluid in which circulating red cells are suspended seem difficult to believe in view of the author's statement that changes in plasma volume were generally unrelated to the presence or absence of anemia It would be of great interest to have parallel measurements of the red cell volume as measured by tagged red cells —Ed]

Idiopathic Hypochromic Anemia in Young Adult Males During the past two years P H Shorthouse and R C King[1] observed 20 cases in soldiers aged 18 23 All but one had been in service for less than three months Questioning revealed no relevant history or abnormal food habits No gross organic disease evidence of gastrointestinal hemorrhage or bleeding hemorrhoids were noted Most patients showed a definite tendency to immaturity Nail changes were present in seven and splenomegaly in four Hemoglobin levels ranged from 6 3 to 11 Gm /100 ml and red cell counts from 3 500 000 to 5 200 000 There were achlorhydria or hypochlorhydria in 16 patients hyperchlorhydria in 3 and normal gastric acidity in 1 The blood picture of most patients rapidly improved to

(1) Brit M J 56 259 Aug 4 1951

normal when they were treated with bed rest normal diet with vitamin supplements and adequate amounts of iron

There was no indication that these anemias resulted from blood loss However failure to demonstrate blood loss does not eliminate the possibility of its occurrence in the past Three patients had symptoms or signs suggesting the presence of anemia before military training was begun A combination of factors has probably depleted the amount of iron available for hemoglobin synthesis Deficiency of hydrochloric acid in gastric secretions was likely one of the factors although not the primary cause since four patients were not achlorhydric The extra physical exertion involved in basic training may have been sufficient to produce symptoms in subjects pre viously anemic but hitherto symptomless There is however a further possible explanation Usually the first few months of a recruit s life are accompanied by considerable weight gain partly due to enhanced development and hypertrophy of the musculature This change is more pronounced in those previously immature and of poor physique Possibly the ab normal demand for iron cannot be met by increased intake because of defective intestinal absorption and iron for the enhanced development is obtained at the expense of blood hemoglobin Thus either anemia is produced or latent anemia becomes obvious

[The authors reasoning is excellent However hypoch om c anemia an adult male should always raise the question of and result in tests for occult blood loss —Ed]

OTHER ANEMIAS

Chronic Anemia with Arrest of Normoblastic Maturation (Blackfan Diamond Type) is reported by Marcel Lelong R Joseph Cl Polonowski G Desmonts and J Colin[4] in a boy 41/ followed over 2 years The condition characterized by intense erythropenia probably congenital resists all treatment except blood transfusions which have an immediate but transient effect and which because they must be given re peatedly frequently lead to hepatomegaly and hemosiderosis Despite the intensity of the reduction of erythrocytes prog nosis is not bad so long as transfusions can be given From comparison of the blood and bone marrow counts of their

(4) A b f c p d t 8 473-485 1951

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(3) B r M J 2 256 259 Aug 4 1951

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(4) A h f c p d t 8 473 485 1951

patient, the authors discovered an additional characteristic of this condition despite peripheral erythropenia the bone marrow is rich in young cells which do not however develop into adult red cells no intermediate cell appears and there is apparently an arrest of normoblastic maturation which might be called erythrogenesis imperfecta

Boy 4½ born at term of healthy parents showed pallor at [?] months but since growth was normal did not arouse anxiety At 2 years 2 months pallor was extreme The first blood count showed anemia (red cells 1 000 000) resistant to all forms of treatment except blood transfusions which increased the red cell count only temporarily Nearly 60 tran fusions were given in three years leading to hemo iderosis with liver enlargement and cutaneous pigmentation Nevertheless growth and development were satisfactory and the child was active happy and psychically normal

Pallor is the principal and for a long time the only symptom of this chronic hypoplastic anemia Though the blood count in this child showed only intense erythropenia without signs of regeneration the bone marrow taken either from the sternum or the iliac crest was always rich in elements of the three series But about 90% of the erythroblasts were young normoblasts still basophilic whereas the number of polychromatophilic or acidophilic normoblasts was greatly diminished Maturation was evidently arrested with the basophilic normoblasts The insufficiency of their development was confirmed by anomalies in the chromatin contained in their nuclei and the fragility of their cytoplasm whereas the polychromatophilic and acidophilic normoblasts were cytologically normal

Despite its severity anemia of this type is remarkably well tolerated with regular transfusions its cour e may be prolonged for years Normal hemopoiesis has apparently been established in some cases resulting in spontaneous cure

Anemia of Renal Insufficiency as Induced by Bilateral Nephrectomy of Rabbit With Emphasis on Its Hemolytic Nature In the course of utilizing bilaterally nephrectomized animals in study of cardiovascular disease E E Muirhead Frances Jones and Arthur Grollman[5] (Southwestern Med School) noted development of severe anemia in the animals Examination of the spleen mesenteric nodes and liver showed hemosiderosis and erythrophagocytosis which suggested an intracellular hemolytic process

(5) J Lab & Clin Med 39 505 517 April 1952

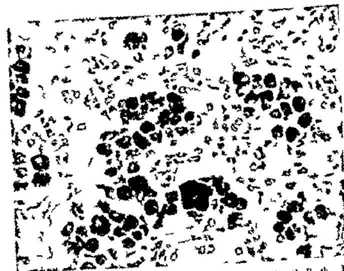
To identify the extent mechanism and characteristics of this anemia bilateral nephrectomy was performed on rabbits Rapid development of anemia was observed together with rapidly developing extreme azotemia The anemia was identified by lowering of the hematocrit reading erythrocyte count hemoglobin concentration and decrease in red cell volume by the T 1824 dye and P^3 methods That the anemia was not due to blood loss was shown by low iron content of stools and absence of hemorrhage at autopsy The rapidity with which the anemia developed in the absence of blood loss indicated that a hemolytic process was involved as did elevated serum bilirubin and biliary pigment content of stools elevated serum iron concentration and elevated saturation limit for iron in the serum Bone marrow of several animals contained a normal or elevated percentage of normoblastic elements Finally increment in content of iron in the spleen was of such magnitude as to indicate accelerated breakdown of red cells The hemolytic system involved in the observed hemolysis was not elucidated although the frequent observation of erythrophagocytosis in tissues rich in reticuloendothelial elements in the dog under similar circumstances suggests strongly a phagocytic or intracellular form of red cell destruction The greater degree of siderosis in the spleen in the rabbit as well as in the dog is an additional feature supporting this view The hemolysis was not associated with reticulocytosis which indicated the simultaneous occurrence of suppression of marrow and failure of acceleration of delivery of young red cells to the circulation Suppression of marrow function however must be relegated to a secondary *role in view of the rapidity of development of the anemia* Neither leukocytes nor platelets were decreased in these animals

[This experimental study of the anemia of renal failure sheds light on a clinical topic as yet insufficiently studied. F H Gardner has shown the beneficial effects of cobalt therapy on the anemia of some of these patients —Ed]

Essential Pulmonary Hemosiderosis B Jonsson B Vahlquist and K Agner[6] (Stockholm) report a case The fundamental cause of this disease is unknown The typical picture is of involvement of the lungs and anemia Characteristically

(6) Blood 6 665 671 July 1951

there are no evidence of heredity even sex distribution onset almost always in childhood long standing course serious prognosis (many cases are fatal) relapsing attacks with hemoptysis simulating pulmonary edema and eventually chronic insufficiency with dyspnea and cyanosis In the lungs autopsy shows diffuse bleeding due to diapedesis hemosiderosis and changes in elastic tissue of blood vessels Blood picture is of iron deficiency anemia with pronounced reticulocytosis



Blood 6 665 671 July 1951)

sis There is no general bleeding tendency During attacks serum bilirubin and urine urobilinogen values may be elevated Iron therapy is often beneficial Patients with severe chronic lung insufficiency may have polycythemia

Boy 5 had a history of undiagnosed anorexia three years previously At 4½ he became increasingly tired and pale Hemoglobin value was 3 7 Gm /100 cc Thereafter hypochromic anemia and increased reticulocytosis persisted He improved temporarily as a result of blood transfusions but iron liver extract and folic acid were ineffective At 5 fever cough pronounced dyspnea and increased anemia appeared Chest x rays showed small patchy shadows which decreased in a few weeks two months later he had another attack with hemoptysis Examination showed pronounced pallor increased pulse rate and a soft systolic murmur

in the second left interspace Except for severe hypochromic anemia blood studies were normal including the direct Coombs test and tests for hemolysins in serum Marrow puncture revealed normal leukopoie is but small pale red cells which showed anisocytosis and moderate poikilocytosis Rapidly proliferating immature erythroblasts were reduced in number and Howell Jolly bodies and mitosis were lacking Urine and stools were normal

The condition remained stationary for a few weeks Then a new attack occurred and about 100 cc blood was lost by hemoptysis Urobilin increased in the urine and serum bilirubin value rose This attack subsided in a few days Two days after the last hemoptysis wide pread miliary shadows appeared in chest x rays Later x rays improved somewhat X rays of other organs were normal (heart liver spleen skeleton) By differential agglutination it was shown that cell from the last transfusion disappeared completely after 33 days A month later he had another hemoptysis and died in a few hours

At autopsy the lungs were large and consi tency was increased There were many small dark red petechiae on the pleura The cut surface was somewhat hard but smooth and homogeneous There was no pus in the bronchi and there were no changes in other organs Microscopic sections showed alveoli crowded with large cells the cytoplasm of which contained brown pigment Laked red cells were in other alveoli The walls between the alveoli were increased in thicknes with dilated capillaries slightly fibrosed and contained numerous hemosiderin macrophages (Fig 61) The elastic tissue of small and medium pulmonary arteries formed coarse thready structures Chemical analysis showed that hydrolyz able iron in the lungs was increased 100 times above normal mainly as hemosiderin in the cells it apparently had not been available for blood regeneration

[Those interested in blood d sorders should be aware of this little understood condition —Ed]

ACTH and Cortisone in Treatment of Aplastic and Adynamic Anemias is presented by Theodore H Spaet Martin C Rosenthal and William Dameshek[7] (New England Center Hosp) in 19 patients aged 4-73 years whose symptoms had lasted two weeks to 17 years before treatment All patients were hospitalized for study which included blood counts marrow aspirations and other diagnostic tests as indicated

Of 11 patients with classic findings of aplastic anemia with a profound pancytopenia only 2 gave a history of exposure to chemical agents One had repeated inhalations of gasoline products the other (a soldier in the South Pacific

(7) B H N w E al d M C r 13 25 263 Dec mbe 1951

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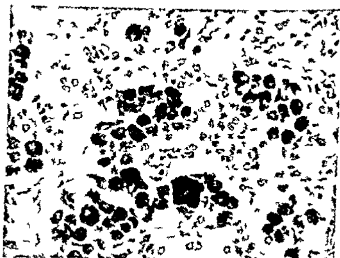


Fig 61 —H m d n ma oph g l g t St n d w th P th B l t (C u t y f J on B f l Blood 6 665 671 J ly 1951)

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Pulmonary Function Studies in Polycythemia Vera Results in Five Probable Cases are reported by Walter Newman James A Feltman and Blanche Devlin[8] (V A Hosp Bronx N Y) Measurements were made in each case before and after phlebotomy of (1) residual air volume and intrapulmonary mixing (2) lung volume (3) maximal breathing capacity (4) arterial oxygen content and capacity and carbon dioxide content (5) oxygen consumption (6) pH of blood and (7) blood volume by use of P^{32} labeled red cells

Arterial blood samples and expired air (for oxygen consumption) were collected in the basal state with the patient breathing room air and high and low oxygen concentrations each for 25 minutes In addition oxygen saturation was determined after one minute of standard exercise during which oxygen consumption was also measured and respiratory rate and tidal air values were obtained

In all five cases maximal breathing capacity increased after phlebotomy (table) a finding attributed to increased elasticity and decreased viscous resistance of the lungs and a decrease in anoxemia In Cases 1 and 2 this was the only change In Case 3 the patient who could hyperventilate well showed pronounced arterial desaturation during exercise owing to failure to increase ventilation significantly and as a consequence inadequate oxygen consumption This occurred despite a low pH high arterial pCO_2 and anoxia the respiratory center was apparently insensitive to these stimuli After phlebotomies ventilation and oxygen consumption during exercise and arterial oxygen saturation after exercise became normal Effective alveolar ventilation at rest remained elevated

In Case 4 vital capacity total capacity and maximal breathing capacity were greatly reduced Before phlebotomy the patient had a distribution gradient indicative of perfusion of poorly ventilated areas Marked arterial oxygen desaturation which was present at rest was probably due to inadequate ventilation venous admixture and respiratory center

(8) Am J M d 11 706 714 D mb 1951

area) had been given prolonged prophylactic treatment with atabrine*

Two patients had typical acutely developing aplastic anemia apparently due in one to idiosyncrasy to sulfonamides and resulting from miliary tuberculosis in the other The other six patients had varying degrees of anemia with or without depression of leukocytes or platelets their marrow showed adequate or increased cellularity No cause could be found for the condition

All but the two patients with acute condition had been treated before with liver extract iron and repeated blood transfusions None had responded to any treatment or shown a remission except possibly one who may have had a remission after sterilization for uterine hemorrhage

ACTH was given subcutaneously every six to eight hours 45 200 mg daily Cortisone was given intramuscularly or orally When given by mouth the dose was 50 300 mg in two to four doses The hormones were given for periods of a few days to over a year Three patients with adynamic anemia and one with aplastic anemia had splenectomies after cessation of hormone treatment Follow up studies (several months to over a year after treatment) were obtained in most instances

Among the 11 chronic cases one patient with aplastic anemia has maintained clinical hematologic and marrow remission at time of the report (more than 13 months) while given cortisone

Two other patients showed increased white cell count and granulocytes while the hormone was administered In one of them the improved marrow changes were notable and persisted after hormonal treatment had been stopped wherea the peripheral blood picture showed little improvement The hormones were ineffective in all other cases including the two cases of acute aplastic anemia

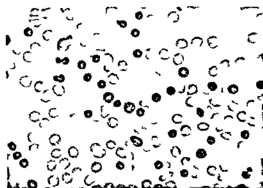
Splenectomy in four patients with chronic adynamic anemia resulted in partial response in two patients in one the improvement has been maintained over six months

Although the over all result is poor the one dramatic response has encouraged the authors to suggest that continued trial with these hormones is indicated particularly as long as no other effective treatment is available

respiratory center damage thus initiating a vicious cycle Since these changes apparently are reversible only in the beginning stages early treatment of the disease is indicated

[The hematologic findings in these patients would appear to be consistent with polycyth mia vera particularly as either before or especially after phlebotomy in four patients the percentage saturation of the arterial blood was normal and in the fifth is known to have been so at a time when the patient was polvcythemic The ventilatory abnormalities found seem to re ult from rather than to be primarily causative of the increased erythropoiesis and may well in turn contribute to its augmentation Here then in the e patients i primary polycythemia vera complicated by a vent latory d fect capable of causing s condary polycythemia —Ed]

Erythremic Myelosis in Girl Aged 13 Years Neoplastic change in the primitive red cells analogous to that of myeloid leukemia is to be expected but such cases are rare Only 8



F p 6 —P ph l blood T f d yth ocy ly d t g h d f m t t ll M y yth bl t G m ta × 600 (C t y f Em ry J L P h & B ct 63 395 40 J ly 1951)

or 12 accepted cases are in the literature which has been reviewed by Moeschlin (1940) di Guglielmo (1946) Mallarme and Moulonguet (1947) and Leitner (1949) John L Emery[9] (Sheffield Children s Hosp) describes a patient whom he believes had this disease

Girl 13 was ho pitalized with a six week history of pallor and bleed ng Examination of peripheral blood revealed many erythroblasts (Fig 62) at on tim 550 000/cu mm These were abnormal normoblasts of average diameter (11 μ) and did not mature on culture in vitro Bone marrow wa almost entirely filled with large

(9) J I h & P t 63 395 40 I ly 1951

damage (Although the patient could ventilate quite well and had several other stimuli for hyperventilation he failed to hyperventilate at rest) Ventilation gas exchange lung volume and arterial saturation became essentially normal after phlebotomy

Pulmonary function changes in Case 5 were much like those in Case 4 except that there was a high diffusion gradient This may have been due to a reduction of the diffusing surface by thrombosis Persistence of anoxia after phlebotomy

RESULTS OF PULMONARY FUNCTION STUDIES BEFORE AND AFTER PHLEBOTOMIES* IN FIVE CASES OF POLYCYTHEMIA VERA

	Hemoglobin Gm /100 Cc	Blood Vol Cc		Art O Sat † %	Art O Sat after Exercise †
		Actual	Predicted		
Case 1					
Before	22 0	10 000	3 960	94 4	94 4
After	14 6	7 500	3 960	95 0	94 0
Case 2					
Before	20 1	6 300	4 800	95 5	98 0
After	14 5	5 750	4 800	97 0	96 0
Case 3					
Before	23 6	7 930	3 890	95 4	75 0
After	15 0	5 360	3 890	95 8	95 0
Case 4					
Before	23 0	—	—	69 0	—
After	15 7	—	—	95 4	93 7
Case 5					
Before	21 8	8 450	5 020	65 0	60 6
After	16 3	7 900	5 020	80 3	86

* Case 1 2 85 L in 21 days Case 2 2 5 L in 21 days Case 3 3 7 L in 30 days Case 4 5 4 L in 32 days and Case 5 4 8 L in 60 days
† Normal 94 98%

was probably due to continued poor correlation between ventilation and perfusion i e poor effective alveolar ventilation due to respiratory center impairment The patient utilized only 7 6 of his maximal breathing capacity when arterial pO_2 was 51 mm Hg and pCO_2 66 mm When he was placed in a Drinker respirator for two days arterial pCO_2 dropped to 53 mm and oxygen saturation rose to 93% However within one hour after he was removed from the respirator the values reverted to the previous levels

The authors concluded that in polycythemia vera changes in ventilation and gas exchange may occur with development of severe anoxia Anoxia and other unknown factors cause

respiratory center damage thus initiating a vicious cycle Since these changes apparently are reversible only in the beginning stages early treatment of the disease is indicated

[The hematologic findings in these patients would appear to be consistent with polycythemia vera particularly as either before or especially after phlebotomy in four patients the percentage saturation of the arterial blood was normal and in the fifth i known to have been so at a time when the patient was polycythemic The ventilatory abnormalities found s em to result from rather than to be primarily cau ative of the increased erythropoiesis and may well in turn contribute to it augmentation Here then in these p tients i primary polycythem a vera complicated by a vent latory defect capable of cau ing secondary polycythemia—Ed]

Erythremic Myelosis in Girl Aged 13 Years Neoplastic change in the primitive red cells analogous to that of myeloid leukemia is to be expected but such cases are rare Only 8

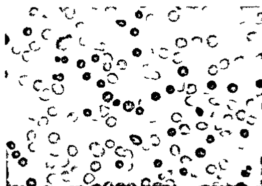


Fig 6 —P ph l blood T f ed yth y l d t gu h d f om p t t ll M y yth obl t G m ta × 60) (Court y f Em ry J L J P h & B ct. 63 395 40 J ly 1951)

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(9) J P h & B t 63 395 40 J ly 1951

polychromatic normoblasts Leukocyte and platelet formation was depressed but these elements were in normal ratio to each other Laboratory studies did not provide evidence of a hemolytic factor Folic acid therapy was not beneficial Removal of an enlarged spleen did not alter the course She was kept alive for 2½ years by repeated blood transfusions Immediate cause of death was sepsis and hemorrhage

At autopsy in addition to the marrow changes areas of erythroblastic infiltration were seen in the liver pancreas and kidneys Diagnosis was considered to be polychromatic normoblastic erythremic myelosis

[Because polycythemia vera is considered by some to be a neoplasm of erythropoietic tissue it is interesting that this patient was either not observed while in the polycythemic phase or never exhibited it The peripheral leukopenia and lack of granulocytopoietic hyperplasia of the bone marrow are also thought provoking differences as is the rarity of polycythemia vera in the second decade of life —Ed]

Evaluation of Radiophosphorus Therapy in Primary Polycythemia In the past decade radiophosphorus (P^{32}) has become widely accepted for treatment of this condition Charles F Stroebel Byron E Hall and Gertrude L Pease[1] (Mayo Clinic) report on 199 patients so treated and 32 others treated by phlebotomy phenylhydrazine and roentgen radiation

Three general types of primary polycythemia were noted (1) polycythemia characterized by increased erythrocyte volume and normal or increased blood volume (2) polycythemia with panmyelopathy and (3) the first or second type plus a history of vascular accidents Therapy other than P^{32} had been given 96 (48%) mainly bleedings and phenylhydrazine Accurate comparison of results with those of later P^{32} treatment was not possible but all patients so treated were in relapse and previous treatment had failed to produce remissions of a year or more

The method of treatment consists of reducing the hematocrit to 55% or less by repeated venesection then giving intravenously 5 7 mc P^{32} as dibasic sodium phosphate in sterile saline The patient returns for blood examination at intervals of six to eight weeks When polycythemia recurs P^{32} therapy is repeated In the present series to obtain successful remissions on the average a course of 9 10 mc was required The average remission lasted 1 6 years

(1) J A M A 146 1301 1307 Aug 4 1951

Causes of deaths of the 32 patients treated by means other than P³ are given in Table 1 Deaths from vascular accidents tended to occur within the first decade and those from leukemia usually occurred later However the inci dence of earlier leukemia may have been masked by the high mortality from vascular accidents Evaluation of P³

TABLE 1—CAUSES OF DEATH OF 3 PATIENTS WITH PRIMARY POLYCYTHEMIA TREATED BY MEANS OTHER THAN P^{32}

	No	%
Thrombosis		
Coronary	8	25 0
Mesenteric	3	9 4
Hepatic vein	1	3 1
Hemorrhage		
Cerebral	3	9 4
Gastrointestinal	3	9 4
Chronic myelocytic leukemia	4	12 5
Malignant tumors	4	12 5
Peritonitis	2	6.2
Others	4	12 5

TABLE 2—CAUSES OF DEATH AMONG 148 PATIENTS WITH PRIMARY POLYCYTHEMIA TREATED WITH P³

	No	%	
Acute leukemia	4	2 7	
Chronic myelocytic leuk mia	1	0 7	
Aplastic anemia	1	0 7	
Congestive heart failure	2	1 4	
Coronary thrombosis	3	2 0	4 7 (Coronary thrombosis + Cerebrovascular acc dents)
Cerebrovascular acc dents	4	2 7	
Malignant tumors	3	2 0	
Pneumonia	1	0 7	
Postoperative hemorrhage	1	0 7	
Unknown	2	1 4	
	2[illegible]	15 0	

therapy was based on 148 patients 22 of whom died (Table 2) So far there has been a decided reduction in vascular accidents in this group The incidence of leukemia and other hematologic complications was small compared with that of vascular accidents in the pretreatment group Seventy five per cent of the patients had remissions of over one year and 90% were considered successfully treated Occurrence of leukemoid reactions or hyperuricemia in patients with some panmyelopathy reduced the incidence of success to some degree

Effect of Intravenous Histamine Administration on Level of White Blood Count in Peripheral Blood is discussed by Howard R Bierman Keith H Kelly Nicholas L Petrakis Fauno Cordes Marilee Foster and Elizabeth A Lose The pulmonary circulation has been shown by infusion methods to contain a mechanism able to remove leuko ytes from peripheral blood In experimental anaphylaxis a histamine like substance is presumably released respiratory difficulty ensues and striking leukopenia promptly appears together with sequestration of many leukocytes in the pulmonary capillaries Because of the similarity of histamine reactions and anaphylactic shock the former was studied Leukopenia may be extreme is usually transient and preinjection levels are generally regained in 10 15 minutes

METHOD—Twelve patients with various advanced metastatic neoplasms were chosen A cardiac catheter was usually passed into the right ventricle or pulmonary conus A no 18 or 19 needle was placed in the brachial artery of the opposite arm Histamine base 0 1 0 3 mg as the phosphate (2 75 mg /cc = 1 0 mg base) diluted 1 10 with saline solution was injected intravenously over 10 60 seconds Arterial and venous samples were taken simultaneously at frequent intervals during and for 10 30 minutes after injection They were placed in 5 cc tubes with 2 mg liquid heparin White cell counts were done promptly Clotting tim s were determined in both glass and silicone lined tubes

Fourteen investigations were done on 12 patients White cell counts fell promptly in all but two with no significant variation in red cells platelets or hematocrit reading The fall was transient the level returning toward the original in 3 10 minutes An arterial venous difference in number of cells occurred primarily in neutrophils because of the larger number of these cells involved although a similar percentage decrease in lymphocytes was found in 8 of 10 patients with leukopenia White cell counts of arterial blood exceeded those of venous blood during return toward the control level Silicone clotting time decreased greatly immediately after intravenous administration of histamine in the three patients in whom it was studied

(2) Blood 6 9 6 935 O t be 1951

White cells decreased in the arterial blood 20 180 seconds (at least one to two circulation times) before the fall in venous blood count This indicated that the leukocytes were being withdrawn between the venous and arterial sampling sites which were chosen so that the lungs were practically isolated The lungs retained the cells for only 50 150 seconds and then began delivering them to the arterial system

The two patients in whom the leukocyte level was unaffected had only negligible respiratory symptoms One of them had lymphosarcoma with 14 000 white cells (16% leukocytes) and had not received treatment The other had lymphatic leukemia with 185 000 white cells Likewise the only patients who failed to show a removal mechanism in the lung as demonstrated by cell infusion or cross transfusion technics were also leukemic

Under the conditions of this investigation the lungs maximally remove an average of 720 white cells/cu mm / minute or a total of about 4 billion white cells during this time White cell counts of arterial and right ventricular blood normally show a variation indicating flow of cells into and from the lungs which may reflect the control exerted to maintain homeostasis of the white cell count

Abnormal Lymphocytes ("Virocytes) in Virus Diseases Other Than Infectious Mononucl osis Although the abnormal lymphocytes occurring in infectious mononucleosis are characteristic they are not pathognomonic for they are seen in other virus diseases also They appear at various intervals after onset of infectious mononucleosis Joseph Litwins and Sidney Leibowitz[3] (Beth Israel Hosp New York City) noted them the first day in 1 of 25 consecutive patients with sporadic cases average day of appearance was 9 8 In all but one case maximal percentage of lymphocytes was over 60 over 10% of which were abnormal Abnormal lymphocytes were noted for as long as 286 days Cells of each of Downey s types (I II III) were noted The authors believe that the type III cell which is rarely seen is consistently observed for brief periods early in the disease and that the three types are not exclusive of each other but rather represent transitions from one to another

(3) A t h m t S 3 231 Ap l 1951

Of 55 patients with viral hepatitis (both serum and infectious) 29 showed abnormal lymphocytes but in lesser numbers and for shorter periods than in infectious mononucleosis The cells seldom persisted beyond the first few weeks Transition of cell types was noted in the few cases in which early and serial examinations were made Earlier or more frequent examinations might have revealed more patients with abnormal lymphocytes

Similar abnormal lymphocytes were noted in 13 patients with virus pneumonia in 2 infants with roseola infantum in 1 adult with herpes simplex (febrilis) and in 4 adults with herpes zoster during the height of illness In none did they exceed 10% Others have noted such cells in rubella rubeola influenza type B upper respiratory infections undulant fever rickettsialpox allergic states coronary artery disease and in apparently normal persons When observed unassociated with obvious virus infection the cells should initiate a search for such an infection

The authors propose the term virocyte for this abnormal lymphocyte

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LEUKEMIAS AND RELATED DISORDERS

Relative Rates of Formation of New Leukocytes in Patients with Acute and Chronic Leukemias Measured by Uptake of Radioactive Phosphorus in Isolated Desoxyribosenucleic Acid Edwin E Osgood Harold Tivey Kenneth B Davison Arthur J Seaman and Jonah G Li[4] (Univ of Oregon) treated patients with leukemic leukemia with P^{32} according to a schedule previously outlined and studied uptake in desoxyribosenucleic acid isolated from leukocytes

Rate of new cell formation in patients with either chronic granulocytic or subacute monocytic leukemia was adequate to produce complete labeling of the desoxyribosenucleic acid phosphorus of the cell population in seven days From this it may be inferred that life span of leukocytes in patients with these diseases is of the order of three days

Rate of new cell formation in patients with chronic lymphocytic leukemias was so slow that it was estimated that

(4) Ca e 5 331 335 Ma h 1952

100 days would be required to renew the cell population This implies a life span of the order of 30 days for the leuko cytes In contrast two patients with acute lymphocytic leuke mia showed P^{32} uptake rates by desoxyribosenucleic acid which indicated complete new cell populations in less than seven days Thus a biochemical method of estimating degree of acuteness or chronicity of leukemias is available and may prove useful

[These rates are much slower than was suggested by cross circulation experiments such as those of J S Lawrence from which it was con cluded that normal leukocytes are replaced about 1½ times in 24 hours —Ed]

Latent Hemolytic Syndrome in Leukemia with Splenomeg aly is discussed by Ragnar Berlin[5] (Univ of Uppsala) It has long been believed that an enlarged spleen inhibits function of bone marrow probably by humoral transmission However presence of hyperactive marrow jaundice or increased urobilin excretion and reticulocytosis indicates that hemolysis must be expected in hypersplenic conditions Recently better in sight into the problem has been obtained by studying red cell elimination in vivo With Ashby s differential aggluti nation method the fate of transfused O cells can be followed in an A B or AB blood group host and group O can be studied with the M N or Rh system Normally transfused cells disappear linearly in about 120 days In hemolytic anemias however survival times are shorter and the elimina tion curve is usually exponential Survival time was greatly reduced in all 10 cases of leukemia associated with splenomeg aly (Fig 63) In one patient with myeloid leukemia after splenectomy red cell survival time was normal The anemia also disappeared This proves clearly that the hypersplenic anemia in these cases results wholly from increased destruc tion of blood

Initially in myeloid and occasionally lymphatic leukemias an unequivocal leukemic blood pattern and splenomegaly are usually present The red cells and platelets are not particularly affected and there is no jaundice or other obvious sign of in creased destruction of blood On the other hand moderate reticulocytosis is often and urobilinuria always present Only after some time does anemia appear A latent hemolytic syndrome must be considered in these patients demonstrated

(5) Acta med scand 139 331 340 1951

if possible and when conditions are suitable corrected by splenectomy Whether the strictly leukemic process can be reversed is unknown Operation is indicated in early cases of severe hemolytic anemia when marrow is not affected by leukemia and in cases associated with pronounced hemorrhagic diathesis and thrombocytopenia It is of paramount importance that it be undertaken early and after the spleen has first been shrunk by means of urethane or x ray treat

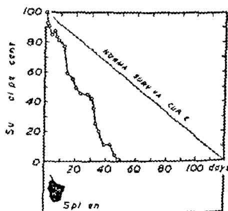


Fig 63—Survi l t me f t n fu ed ed ell n h molyt a m a (Court f Be l n R A ta m d cand a 139 331 340 1951)

ment The future will show to what extent splenectomy carried out in time and in carefully selected cases will give better long term results

[Increased red cell destruction in patients with leukemia may not be associated with reticulocytosis and jaundice as has recently been clearly demonstrated by Ross —*Ed*]

Unusual Anemia Associated with Chronic Myeloid Leukemia Lawrence E Young Richard F Platzer (Univ of Rochester) and John S Lawrence[6] (Univ of California) report a case which was observed 14 months before leukemia was diagnosed

Woman 50 had been frail all her life and had been told she had anemia *for 15 years but there were no definite records* of it until 2 months before she was first seen by the authors *Except* for pallor and slight malnutrition the only physical abnormality was a pronounced hemic murmur over the entire *precordium* Red

(6) Act ha m s 5 345 359 J 1951

cell count was 2 780 000 hemoglobin 5 9 Gm hematocrit 25% reticulocytes 3 5% and white cell count 4 300 with 61% lymphocytes and no shift in granulocytes Platelets were normal Red cells showed extreme variation in osmotic fragility size shape and hemoglobin content (Fig 64) A few target cells were present Results of the Coombs Ham Donath Landsteiner and sickling tests were negative Bone marrow contained 74% erythroid cells (normoblastic series) and 21% myeloid cells with no appreciable shift to the left Gastric juice contained no free acid after injection of histamine X rays of the gastrointestinal tract revealed only a small diverticulum in the midesophagus

She was given 0 8 Gm ferrous sulfate daily for 90 days and



Fig 64 (left) —St k g t hap d d g f hyp h m f d ll W ght t d d f m × 1500
Fig 65 (right) —F rt mo th l t N m my l yt th mb yt p d ta g t ll W ght t d d f m × 970
(C t y f Y g L E t l A t h m t 5 345 359 J 1951)

8 5 mg folic acid daily for 50 days with no response Four months after initial observations a few spherocytes and normoblasts were first noted in peripheral blood and target cells were increased Mechanical fragility of red cell was significantly greater than normal Examination of sternal marrow again revealed striking normoblastic hyperplasia and little shift in myeloid elements Because of persistent reticulocytosis increased fecal urobilinogen excretion and normoblastic hyperplasia of marrow erythrocyte life span was considered to be shorter than normal Although the red cell differed from those of hereditary spherocytosis splenectomy was performed six months after she was first seen Some hemosiderin was found in the spleen but erythrophagocytosis was not evident The pulp was not engorged with red cells as it is in hereditary spherocytosis

After operation anemia persisted target cells and normoblasts

became more numerous and red cells became still less fragile to hypotonic saline solution whereas mechanical fragility remained greater than normal Fourteen months after the first examination she became weaker and hepatomegaly edema of the ankles ecchymoses and several cutaneous nodules developed White cells rose to 169 000 and there were pronounced thrombocytopenia decided shift to the left in the myeloid series and 26 normoblasts/100 white cells (Fig 65) Sternal marrow was highly cellular and showed preponderance of myeloid elements White cells increased steadily to 244 000 She gradually became weaker and died a month later Diagnosis of *myeloid leukemia was substantiated* at autopsy

In retrospect the extensive myeloid metaplasia found in the spleen at operation could be considered early leukemic alteration which suggests that the patient actually had leukemia when the anemia was first detected as the earliest sign of leukemia Although moderate changes in red cells are found in myeloid leukemia in no other case have the authors found leptocytosis comparable to that seen in this patient nor has pronounced anemia preceded the making of the correct diagnosis by such a long period The authors believe that in many cases anemia is not adequately explained by displacement or destruction of erythrogenic tissue in the marrow blood loss or destruction of red cells by the action of extracorpuscular factors They assume that this patient had a single hematologic disease chronic myeloid leukemia and that disorderly erythropoiesis was an unusually early manifestation of the leukemic process It is hoped that investigation of additional patients showing comparable abnormalities may ultimately clarify the pathogenesis of anemia in these cases and its relation to myeloid leukemia

[This degree of variation in hemoglobin content of red cells in a patient with leukemia is most unusual Because no records of earlier blood examinations existed an underlying disturbance such as Mediterranean anemia was not absolutely excluded —Ed]

Hypocellular Marrow in Acute Leukemia Report of Two Cases is made by Milton R Beyers Leo M Meyer Martin Lowenthal Robert J Oehrig and Arthur Sawitsky[7] (New York City) In acute leukemia with or without peripheral leukocytosis sternal marrow aspiration by the Arinkin technic typically reveals pronounced hyperplasia with a predominance of immature blast cells Marrow study is extremely important in differentiating the cases without peripheral leuko

(7) A M A Arch Int M 88 803 811 December 1951

cytosis from cases of aplastic anemia and granulocytopenia The authors report the clinical and autopsy findings in two patients one diagnosed as acute subleukemic myeloblastic leukemia the other as acute monocytoid myeloblastic leukemia at autopsy In both bone marrow aspirations showed hypo cellularity at one time

The finding of hypocellular marrow in acute leukemia in the past was usually explained by failure to hit a hyperplastic nodule on aspiration Alternatively Dameshek suggested that primitive cells adhere more firmly than others to the tissue stroma Whether due to true acellularity or inherent technical error this raises a question as to validity of diagnosis Aspi rated marrow in Case 1 was extremely hypocellular verified on autopsy The scant leukemic organ infiltration seen micro scopically in both cases was interesting Though the marrow in Case 2 was hyperplastic at autopsy hypocellularity was shown eight times before death It seems beyond chance that with this number of examinations a purported patch of hyper plastic cells was never entered Increased stickiness of primitive cells seems improbable since immature erythroid elements are supposedly more adherent than myeloid cells and the 7% of erythroid elements found was the same or higher than the percentage usually noted in typical hyper cellular marrows of acute leukemia [In our experience large cells of the histiocyte (possibly monocytoid as here) type may not be evident in smears from marrow punctures though present in marrow tissue sections —Ed]

The change from hypo to hypercellular marrow in Case 2 and from leukopenia to leukocytosis coincident with relapse suggests that without pneumonia as a presenting complaint the leukemia might not have been diagnosed before it entered the hyperplastic phase Perhaps some patients with acute leukemia have a premonitory hypoplastic marrow phase (not recognized because of lack of associated symptoms) followed by the usual typical picture of hyperplasia Had the first patient lived longer perhaps his marrow would also have be come hypercellular Recipients of transmitted mouse leukemia pass through a leukopenic phase in the peripheral blood and a hypocellular phase in the bone marrow before hematologic and clinical leukemia becomes evident A similar case observed

by two of the authors was not formally reported because folic acid antagonists were used in treatment

Roles of Prothrombin Activity, Heparin Protamine Titer and Platelet Concentration in Bleeding of Leukemia Previously Allen and his associates demonstrated heparin like substances in irradiated dogs after nitrogen mustard poisoning and in idiopathic and leukemic thrombocytopenic purpura Gustave Freeman and John S Hyde[8] (Children s Med Center Boston) carried out heparin protamine titrations on 420 specimens representing 134 subjects including normal controls Of these 228 were taken from patients during episodes of clinically active bleeding and 130 from nonbleeding leukemic patients Titers were normal in the specimens of 81% of nonbleeding and 45% of bleeding leukemic patients Titrations were done on whole blood When the protamine titers were calculated on the basis of unit plasma volume in order to correct for variable degrees of anemia similar distributions of titers for both bleeding and nonbleeding leukemic persons and identical medians for both groups are observed On this basis high titers were found in about half of each group Therefore no positive correlation could be made between elevated heparin protamine titers and bleeding in leukemia Of 18 bleeding subjects with normal protamine titers 11 also had at least 50% of normal prothrombin activity Bleeding thus occurred in leukemic patients with both normal heparin protamine titers and normal prothrombin activity

Plasma fibrinogen concentrations among leukemic children generally were increased over the normal average of 310 mg /100 ml plasma Among 63 specimens from bleeding patients the average was 440 mg /100 ml in only 5 of these was plasma fibrinogen concentration less than 200 mg /100 ml plasma Seldom was a deficiency of fibrinogen associated with clinical bleeding in leukemia

In 351 specimens there was no clinical evidence of bleeding in persons with 55 000 or more circulating platelets/cu mm whereas bleeding was the rule but not invariable among those having fewer platelets Failure to bleed among critically thrombocytopenic subjects was not uncommon 36 of 257 fell within the critically thrombocytopenic range Thus platelet deficiency may be an essential factor but not a completely

(8) Blood 7 311 325 M h 195

adequate cause of bleeding Coagulation (recalcification) time tended to become prolonged when capillary platelet concentrations were about 40 000 50 000/cu mm A few bleeding subjects with critically reduced platelet levels fell within the normal range of coagulation time Obviously the process of coagulation is not invoked without prior insult to the vessel The type of vascular damage associated with thrombocytopenic purpura *may either fail to appear in the presence of* more than 50 000 60 000 platelets/cu mm or be neutralized too rapidly to become clinically manifest A continent vascular bed in the presence of severe thrombocytopenia suggests that other factors may provoke vascular damage Such factors may be operative in the thrombocytopenic state without affecting the recalcification time

Chronic Monocytic Leukemia is reported by J W Beattie R M E Seal and K V Crowther[9] in a woman 58 and a man 55 who lived in good health 3½ years after onset Autopsy observations in the latter are given The first phase was a normocytic normochromic anemia with slight reduction in total leukocyte and neutrophil counts Liver spleen and lymph nodes were not enlarged and the sternal marrow though hypercellular showed no abnormal cells In the next phase the man enjoyed fairly good health with persistence of anemia and development of monocytosis for about two years He then complained of swelling pain on motion and ecchymosis of the lower extremities especially about the ankles where hemarthrosis was thought to exist No blast cells were found in the peripheral blood Most of the monocytes possessed pseudopodia were oxidase positive and in living preparations were *actively phagocytic Similar cells of large size were now* present in the sternal marrow Renal colic though not common in leukemia occurred associated with history of passing a stone which may however have been a blood clot Terminally 3½ years after onset many joints were painful lymph nodes liver and spleen were moderately enlarged There was marked ichthyosis and numerous hard raised nontender red nodules ¼ to ½ inch in diameter were present chiefly on legs and abdomen He died of bronchopneumonia severe gingivitis and many petechiae and ecchymoses

Monocytic leukemia is well recognized in the acute form

(9) Q t J Med 0 131 139 Ap 1 1951

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(8) Blood 7 311 3 5 Ma h 195

generative features of polychromasia and reticulocytosis indicate the etiologic importance of red cell destruction

Several investigators believe monocytic leukemia and the reticuloses are clo ely related and transitions between lymphoblastoma Hodgkin s granuloma lymphosarcoma Hodgkin s sarcoma and monocytic leukemia have been noted No tumor mass was found in either of these cases Nodules in skin kidney and bladder were apparently leukemic infiltrations lymph nodes though histologically resembling Hodgkin s disease had not entirely lost their architecture and phagocytosis was prominent The lymph node in the woman consisted almost entirely of monocytoid cells and was quite unlike nodes in Hodgkin s disease

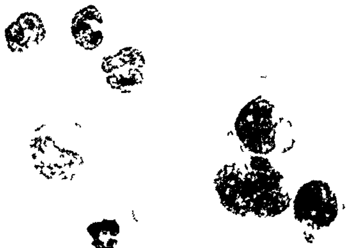
[We should be inclined to call these cases of chronic histiocytic leukemia because of the large size vacuolated cytoplasm and marked phagocytic activity of the typical cells The gradual onset with anemia mild leukopenia normal marrow at first and later arthralgias and infiltrative skin lesions associated with purpura resembl the course in patients seen by us Occasional patients respond to small amounts of bone marrow irradiation even more satisfactorily than do those with chronic myelogenous leukemia —Ed]

Current Trends in Management of Leukemias and Malignant Lymphomas According to Joseph F Ross and Franklin G Ebaugh Jr [1] (Boston Univ) treatment must be directed toward complete surgical removal of neoplastic tissue from or destruction of neoplastic cells in the body Because surgical removal is possible in only a few cases the principal goal is to destroy or inhibit neoplastic growth in the body Available agents destroy normal and neoplastic cells They are effective only because of selective localization or higher sensitivity of the latter The finding of an agent which will destroy only neoplastic cells is the aim of current chemotherapeutic cancer research

Introduction of radioactive isotopes and new chemotherapeutic agents has improved the comfort and usefulness of these patients and their life span has been somewhat prolonged Prognosis depends on the histologic and cytologic characteristics of the tumor and extent and severity of the clinical condition Highly undifferentiated and invasive tumors such as acute leukemia or Hodgkin s sarcoma usually respond poorly whereas chronic lymphatic leukemia or localized Hodgkin s paragranuloma may respond extremely well Fever

(1) M Cl N th Am 35 1381 1401 S pt mb 1951

but chronic cases have rarely been recorded Schilling and others of the trialist school believe that the cell rises from the reticuloendothelial system Several features of these cases support the Schilling concept Large vacuolated blast cells (Figs 66 and 67) in peripheral blood tissues and marrow were unlike blast cells of myeloid or lymphatic leukemia Abnormal differentiation toward the macrophage had occurred and circulating monocytes were more phagocytic toward India



F g 66 (l ft) —Ma ow m a h w ng v cu lated mo oblast and mat mo o ytes × 750
F g 67 (ght) —Vacuol ted mon blast ab matu e m no yt × 1 400 (Co te y f B tte J W t l Q t J Med 20 131 139 Ap l 1951)

ink (not a feature of myeloid or lymphatic leukemia) than normal monocytes Giant phagocytes in medulla and sinuses of lymph nodes suggested a possible origin here with secondary germ follicle invasion The authors believe the leukemic process may commence in lymph nodes or splenic pulp

Chronic monocytic leukemia should be considered in cases of persistent anemia with monocytosis even when primitive cells are absent Cause of the anemia is uncertain Marrow from the man was not hypoplastic or infiltrated with monocytoid cells at a stage when the anemia was well established Hemosiderosis and erythrophagocytosis at autopsy and re

A nitrogen mustard (HN2) when placed in solution forms a cyclic imonium cation which combines with body tissues (chiefly lymphoid bone marrow and enteric mucosa) inactivates certain enzyme systems and causes cell death This action resembles that of radiation in many respects The authors give 2 3 Gm chloral hydrate orally at 8 00 or 9 00 p m and an intramuscular injection of 0 3 Gm sodium amytal® One or two hours later intravenous administration of saline solution is started 0 2 mg HN2/kg body weight freshly dissolved in saline solution is immediately injected into the clysis tubing This procedure is repeated the next night for a total of 0 4 mg/kg Nausea and vomiting often occur 2 4 hours after injection but last only 20 30 minutes if the patient is heavily sedated Leukopenia with profound decrease in lymphocytes reaches a maximum in 6 14 days mild depression in red cells and platelets may be observed after several weeks HN2 causes melting away of the tumor without the initial swelling usually seen after x ray treatment a property of some importance in treatment of tumors situated near the trachea It is of particular value in Hodgkin s disease and reticulum cell sarcoma and of less value in lymphosarcoma and leukemia

Triethylene melamine has the same range of effectiveness as HN2 An hour before breakfast 2 5 5 mg is given orally on two consecutive days and then repeated weekly until remission is induced or depression of hemopoiesis interdicts further therapy

Urethane (2 4 Gm in enteric coated capsules daily) is fairly effective in chronic granulocytic and lymphatic leukemia and multiple myeloma It is the most effective agent available for multiple myeloma Because it causes anorexia and nausea in half the patients given adequate dosage this drug is not as desirable for use in chronic leukemia as radiation therapy

Folic acid antagonists (aminopterin alpha methopterin and dichloroaminopterin) profoundly disturb proliferating cells of the hematopoietic system and gastrointestinal mucosa Aminopterin 0 5 2 mg/day given orally or intramuscularly induces remissions and prolongs life in about half of children with acute leukemia However it is of limited value in adults with any type of leukemia The range between effective and

weight loss anemia and involvement of multiple areas indicate that there will be unsatisfactory response to therapy and rapid progression

Attempts should be made to excise certain lymphomatous tumors when the disease is confined to a surgically accessible area Such procedures are aimed at cure and should be supplemented with chemotherapy and radiation therapy All such cases should be reported regardless of outcome so that statistical information can be accumulated

X rays are external therapy since they must pass through the skin before exerting a therapeutic effect Localized tumors are treated by administering x rays locally in doses of 100-300 r to a total of 1 000 3 000 r Repeated series of treatments are given if necessary Local irradiation of the spleen is the best treatment in granulocytic leukemia associated with pronounced splenomegaly a total series dose of 600 1 000 r being used In leukemia spray or quadrant radiation therapy gives results little better than those obtained by irradiation of the spleen There is little evidence that x ray therapy alone appreciably prolongs life though with antibiotics and transfusions some increase in over all average life span has probably resulted

It is essential for radiation to be delivered as selectively as possible to neoplastic tissue This is achieved somewhat with radioactive phosphorus (P^{32}) which reaches 1½ 2 times greater concentration in neoplastic cells than in normal Also much P^{32} which is retained is eventually deposited in cancellous bone and irradiates the marrow A dose of 6 15 mc (2-4 mc every two to seven days) given by mouth or vein is usually adequate for remission in chronic leukemia lymphocytic types usually requiring less than granulocytic Later 2-4 mc may maintain the white count at 12 000 30 000 and the patient in clinical remission It should be supplemented with x ray therapy for control of local tumor or splenomegaly Improper use of P^{32} causes severe aplastic marrow pancytopenia and thrombocytopenia

Chemotherapy in contrast with irradiation promises far more effective management Fowler s solution 1% arsenic trioxide is still used effectively though arsenic toxicity must often be produced to induce remission

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toxic doses is narrow and extreme caution is necessary to prevent overdosage Treatment is usually given for 21 days or until remission is induced

ACTH 20 30 mg given intramuscularly every 6 hours for 15 20 days or cortisone 100 200 mg given orally or by injection every 12 hours for 15 20 days causes temporary remission in patients with acute leukemia How the remissions are produced is not known Of all the agents discussed only these do not destroy normal tissue cells The brevity of such remissions and the relatively high incidence of complications due to these agents make advisability of their use problematic

Stilbamidine benzol diopterin* teropterin* H 11 K R antireticulocytotoxic serum colchicine myelo and lymphokentric acids are of no practical value in leukemia and malignant lymphoma

Supportive therapy with transfusions control of infections and careful psychologic management are of extreme importance in care of patients with these diseases

[This excellent summary by experienced and objective observers deserves careful study in the original —Ed]

Use of Adrenocorticotrophic Hormone and Cortisone in Treatment of Leukemia and Leukosarcoma is reported by Martin C Rosenthal Richard H Saunders Lawrence I Schwartz Leda Zannos Enrique Perez Santiago and William Dameshek (Tufts College) In 34 patients with leukemia and leukosarcoma treated with ACTH or cortisone ACTH dosage in adults was 15 20 mg subcutaneously every six to eight hours depending on the product used Cortisone dosage was 100 150 mg daily intramuscularly or orally

Of 15 patients with acute or subacute lymphocytic leukemia 3 died (only 1 after adequate therapy) 9 had remissions and 3 did not respond Remissions were heralded by pronounced reticulocytosis followed by increase in red cell count platelets and hemoglobin (Fig 68) Patients with leukopenia regardless of cause had a rise to normal or slightly leukocytic levels whereas those counts already normal or slightly elevated fell with disappearance of lymphocytes and lymphoblasts and secondary rise followed Primitive leukocytes gradually disappeared and the differential became normal with parallel bone marrow changes Remissions ranged

( ) Blood 6 804 8 3 S pt mbe 1951

from 1 to 10 weeks regardless of maintenance therapy after which lymphoblasts anemia and thrombocytopenia recurred Retreatment often induced remissions up to four times but refractoriness developed in every case associated with typical side effects of this therapy

Acute granulocytic leukemia was treated in five adults of whom two were uninfluenced one made moderate improvement and two were worse one dying while on therapy In the latter two rising white cell count and falling platelet count suggested intensification of the leukemic process The patient with favorable response soon relapsed and died six weeks after discharge Two patients with acute monocytic leukemia were in critical condition when treated and died within three days The response resembled that with granulocytic leukemia

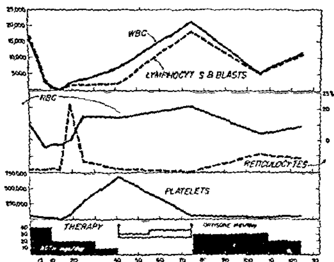


Fig 68—Typical hematologic changes induced by ACTH in subacute lymphocytic leukemia ... fall in leukocytes followed by striking reticulocytosis and thrombocytosis (Courtesy of Rosenthal M C et al Blood 6 804-823 September 1951)

There were five cases of chronic lymphocytic leukemia Two middle aged men were in the terminal phase One had slight improvement in hemoglobin and platelets but the white cell count also rose and the over all picture was not improved

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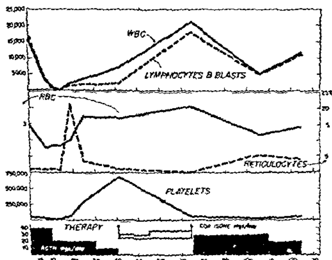
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(2) Blood 6 804 8 3 September 1951

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(2) Blood 6 804 8 3 S pt mbe 1951

ment need not be stopped unless skin lesions appear (6) Alopecia may occur several weeks after start of treatment

Folic acid antagonists alone were given to 59 of the 88 patients with acute leukemia folic acid antagonists and 2 6-diaminopurine to 24 and 2 6 diaminopurine only to 5 Results were evaluated according to age since there is evidence that children have responded more favorably than adults Nineteen of 60 children and 1 of 28 adults had good remissions characterized by return of marrow to normal function and near normal morphology Remissions lasted 4-96 weeks in all but two a second remission was obtained The first reliable sign of impending remission was a decrease in the percentage of leukemic cells and an increase in the more mature myelocytes metamyelocytes polymorphonuclears and red cell precursors in the marrow With one exception marrow reverted to near normal in 20 65 days If remission did not occur in two to three months patients were given 2 6 diaminopurine orally for one to four weeks followed immediately by antimetabolites Once complete remission was produced no further specific therapy was given Improvement was noted in only 4 of the 29 patients receiving 2 6 diaminopurine In addition 10 of 14 patients who improved and then showed resistance to antimetabolites obtained good remissions with cortisone or ACTH Most remissions in children occurred in those whose disease was classified only as stem cell leukemia Leukemia patients with normal or low total leukocyte counts responded better than those with counts over 100 000 From the first appearance of symptoms mean survival time of the 20 patients with good remissions was 16 9 months compared with 4 7 months for 150 similar patients treated before the advent of antifolic therapy

Three of seven children with lymphosarcoma and two with generalized reticuloendotheliosis treated with folic acid antagonists showed significant clinical improvement No consistent or substantial benefits were noted in the other neoplastic diseases studied

Observations on Effect of Various Folic Acid Antagonists on Acute Leukemia are reported by Sloan J Wilson[4] (Univ of Kansas) in 70 patients both children and adults with acute leukemia Five died before adequate data were collected

(4) Blood 6 100 1012 N emb 1951

intramuscularly in saline solution although there is good evidence that at least aminopterin and amethopterin are equally effective by mouth in similar dosage Since therapy must often be continued to the point of relatively severe toxicity and since there is great variation in tolerance each patient must be treated individually Particular care is required in severely debilitated patients and in those with impaired renal and hepatic function Therapy was for the most part given intermittently to allow the patient to recover from induced deficiencies particularly of folic acid Patients were treated until a remission occurred or definite toxic symptoms appeared If toxicity developed treatment was temporarily stopped and later resumed at a lower dosage If a patient failed to improve other forms of therapy alone or combined with antifolic acid antagonists were used These included 2 6 diaminopurine ACTH and cortisone in acute leukemias and nitrogen mustards and roentgen therapy in other forms of neoplastic disease Use of 2 6-diaminopurine an antagonist of adenine was based on the fact that it has proved effective against mouse leukemia and even against a subline of leukemia made resistant to amethopterin Although the authors observed no real therapeutic advantage of one folic acid antagonist over another they generally favored use of amethopterin

Toxic signs usually appear in the following order (1) Whitish or yellowish white necrotic areas develop in the oral cavity or on the lips Healing occurs in 3 14 days after stopping therapy unless secondary infection sets in Anorexia abdominal cramps nausea and vomiting may occur with or even before the oral lesions (2) Hemorrhagic diarrhea may indicate ulcerations in the bowel Treatment should be stopped and the situation re evaluated at the first sign of diarrhea (3) Leukopenia thrombocytopenia and anemia which may appear with or shortly after the mouth lesions are associated with severe bone marrow depression and require transfusions and antibiotics However when these signs are due to the leukemic state they are not contraindications to antifolic acid therapy (4) Increased susceptibility to infections may manifest itself by appearance of furuncles paronychia and in more debilitated patients bronchopneumonia (5) Skin sensitivity reactions usually respond to antihistamines Treat

remissions have occurred no cure of leukemia has resulted from folic acid antagonist therapy

Use of Triethylene Melamine in Treatment of Leukemia and Leukosarcoma Jay H Silverberg (New England Center Hosp Boston) and William Dameshek[5] (Tufts College) treated 46 patients with leukemia leukosarcoma or a related disease with orally administered drug on a fasting stomach Reactions to the drug were mostly gastrointestinal with nausea in about a half and vomiting in about a third of the patients They were usually delayed appearing about eight hours after administration of the drug Slight to moderate depression of hematologic elements particularly those of bone marrow origin was regularly observed with the dosage given Hypoplasia of marrow was noted with long continued ad ministration in Hodgkin s disease Frequent blood cell counts including estimations of platelets are essential when this agent is used

Triethylene melamine was effective in generalized and *radioresistant cases of Hodgkin s disease Remissions occurred* in 30% of 15 patients treated and lasted as long as 164 days The drug was given in divided doses of 2 5 5 mg daily in an initial course of 20 30 mg Recently it has been given more cautiously 2 5 mg every day or every other day After the initial course the patient was observed for two to four weeks and the drug then continued in doses of 2 5 mg twice a week or in a single dose of 2 5 5 mg weekly If the white blood cell count remained at 5 000 or more and platelet counts were normal the drug was continued at weekly intervals Triethylene melamine was as effective as nitrogen mustard in this disease Its greatest advantage over the latter is that it can be given orally Incidence of gastrointestinal reactions is decidedly lower When a rapid therapeutic effect is necessary as in pronounced mediastinal involvement with dyspnea in travenous administration of nitrogen mustard is preferable

When triethylene melamine was given to patients with lymphosarcoma or reticulum cell sarcoma they showed temporary improvement Striking improvement was noted in chronic granulocytic leukemia (eight patients) with great re ductions in white cell count and diminution in splenomegaly in some cases Complete remissions were maintained as long

(5) J A M A 148 1015 10 1 M 2 195

Of the others, 30 had some clinical or hematologic evidence of improvement The following drugs were used intramuscularly or orally aminopterin 0 5 1 0 mg./day a methopterin 3 5 mg /day a ninopterin 1 5 1 0 mg /day and amino an fol 20 30 mg /day There were 38 patients with acute lymphatic 23 with monocytic and 4 with acute myelogenous leukemia

Response most favorable in acute lymphatic and monocytic leukemias consisted of disappearance of lymphadenopathy splenomegaly and hepatomegaly between the second and fifth weeks Remissions ranged from 29 to 490 days and response was generally best in the younger patients No criteria for predicting type or duration of response were noted Some of the best responses were seen in patients most critically ill and vice versa Some of the best remissions however were noted in patients with initial leukopenia

Euphoria and clinical improvement usually preceded hematologic response which started about the third week of therapy with increased platelet level followed by neutrophilic leukocytosis and rise in red cells In 7 of the first 25 patients macrocytosis and anisocytosis developed after 15 30 days of therapy suggesting induction of folic acid deficiency

Effect of the drugs on leukemic cells varied and bone marrow reaction was disappointing even in the 11 patients who responded best in some of them a great number of leukemic cells persisted In a few a rare megaloblast was observed but extremely megaloblastic marrow resembling pernicious anemia developed in only one whose tongue also took on an appearance typical of pernicious anemia

Oral and gastrointestinal lesions were the most common toxic reactions the earliest sign was reddening of the tip of the tongue and the larger papillae Oral mucosal ulcerations were frequent as were smooth tongues and loss of appetite A sprue picture developed in one severe thrombocytopenia in four marrow aplasia in one and alopecia in two The clinical similarity of toxic and leukemic oral and gastrointestinal manifestations made differentiation difficult

Vitamin B_1 and liver extracts were used in most toxic cases but in some the drug was merely discontinued Citrovorum factor may reverse the toxic manifestations of these materials but whether or not it will simultaneously accelerate the leukemic state remains to be seen Although prolonged

notable improvement of erythropoiesis in the bone marrow Three showed no beneficial response Seven patients in series A were treated with amethopterin as soon as relapse was detected after finishing the course of hormones Four of the seven showed no satisfactory response one had slight temporary remission and two appeared to have regained sensitivity

Six children (series B) with acute leukemia were treated with amethopterin after no further improvement could be obtained by hormone therapy In all six remission had been obtained from the first course of corticotrophin (50 100 mg/day) or cortisone (50 200 mg/day) and four patients had second remissions as a result of hormone treatment Four patients had become resistant to hormone therapy in two severe Cushing s syndrome was induced during the second course Series B patients were treated with amethopterin in the same way as the initial therapy for series A Three patients showed a good response one partial remission and two died showing no improvement Further remissions by amethopterin therapy were accomplished in only one of these three patients

That a high percentage of patients respond to hormone or antifolic therapy at a late stage in the course of their disease when resistance to the other method of therapy has developed suggests that corticotrophin and cortisone have a primary mode of action on the leukemic process different from that of the folic acid antagonists Hormones or folic acid antagonists are effective in producing further remissions in approximately 50% of patients showing resistance to one type of therapy This approach may be of further importance if sensitivity to the original form of treatment can be re-established

Splenectomy in Leukemia and Leukosarcoma According to John H Fisher C Stuart Welch and William Dameshek[7] (Tufts College) it is difficult to select leukemia or leukosarcoma patients who will benefit from removal of the spleen and even more difficult to predict degree of palliation Splenectomy was performed in 18 such patients for three indications hemolytic anemia pancytopenia or thrombocytopenia and an enlarged spleen causing great discomfort That 8 of the 18 derived prolonged benefit (one to five years) from

(7) N w E gl d J Med. 246 477 484 M 27 195

as 107 days Doses of 25 mg a week are recommended as maintenance therapy once white cell counts have been reduced to normal

Early results in chronic lymphocytic leukemia (10 patients) indicated that the drug may have its most striking effects in this disease Several patients were maintained for long periods in complete clinical and hematologic remission The course of acute leukemia in adults was unaltered A child with acute lymphocytic leukemia showed striking regression of lymphadenopathy The effect was only temporary however the patient eventually dying

Resistance to Corticotrophin, Cortisone and Folic Acid Antagonists in Leukemia Elizabeth M Kingsley Pillers Joseph H Burchenal Leonard P Eliel and Olaf H Pearson[6] (Sloan Kettering Inst) treated 16 children (series A) with acute leukemia with hormones after no further improvement could be obtained by antifolic therapy Initial antifolic treat ment was usually 5 mg amethopterin daily continued until a remission or toxicity developed Treatment was resumed as soon as toxicity was over provided the bone marrow still showed no sign of a remission It was sometimes necessary to use 10 mg/day whereas other patients tolerated only 25 mg/day Dose was unrelated to the patient s weight or age Once remission was established therapy was discontinued and bone marrow was aspirated once every two weeks Treatment was resumed as soon as the percentage of leukemic cells in the marrow was greater than 15 20% and again continued until another remission or toxicity developed Supportive therapy in the form of antibiotics and blood transfusions was given whenever fever or moderate anemia was present Thus it was often possible to tide a patient over severe toxicity until the bone marrow was able to regain function

All patients in series A had shown remission during treat ment with amethopterin The antifolic therapy was abandoned only when toxic manifestations developed on repeated treat ment without remission In every case the leukemic process showed evidence of progression despite energetic treatment The patient then received cortisone 100-400 mg/day or corticotrophin 50 100 mg/day Ten patients had a good clinical and hematologic response and three others showed

(6) J A M A 148 997 994 March 22 1952

creted as much as 10 20 Gm Bence Jones protein daily whereas others with large amounts excreted little or none However the amount excreted remained roughly proportional to the abnormal serum protein concentration as the disease was treated and as relapses occurred Five patients had no urinary protein and two with widespread disease had no elec trophoretic serum abnormality

Results agree generally with early investigations of these substances Variance in amount and electrophoretic mobility of serum increments shows that those produced by different pa tients with the disease vary in their net surface charge and probably molecular weight The same is true for Bence Jones urinary protein That excreted by a given patient however had either the same or significantly greater electrophoretic mobility than the anomalous serum constituent If mobilities were appreciably different as in nearly half these cases a significant amount of Bence Jones protein in the serum should have produced a second abnormal constituent of faster mobil ity This was not found

To explain the origin of Bence Jones protein the authors suggest that proliferating plasma cells produce protein of ab normal homogeneity and high molecular weight Bence Jones proteins are also abnormally homogeneous and their molecular weight is 1/3 1/6 that of the serum increments As plasma cell growth is suppressed by urethane abnormal serum pro tein and Bence Jones protein decrease and the latter may dis appear The opposite changes occur during relapse Thus Bence Jones proteins seem to be derived from serum incre ments as a fraction of the larger molecules they become filter able through the glomeruli The central phenomenon is ab normal plasma cell proliferation The protein abnormality varies from patient to patient but remains qualitatively con stant once it has developed

Bone Marrow Findings in a Case of Carcinomatosis Re semblance to Myelomatosis is reported by R M Hardisty[9] (Univ of Aarhus)

In a woman 49 with carcinoma of the breast blood studies showed red cells 2 580 000 hemoglobin content 9 Gm /100 cc white cells 3,200 myelocytes 1% metamyelocytes 1% polymorphonu clears 61% lymphocytes 23 per cent monocytes 13% plasma cells

(9) A ta m d dina 142 64 70 1952

splenectomy offers evidence of its value in some instances Three other patients benefited temporarily (3 12 months) Most important in evaluating results is evidence that the *hematologic disorder attributed to hypersplenism has been* corrected Splenectomy controlled hemolytic anemia and relieved cytopenias in most patients Splenomegaly alone is not sufficient reason for splenectomy Operation should be *considered only if there is great discomfort and even then* should be advised only infrequently When hemolytic anemia is the main indication trial with ACTH should be considered as striking improvement may follow ACTH therapy in acquired hemolytic anemia Such treatment should probably precede splenectomy in every instance with surgery reserved for patients who fail to respond

Diagnosis of leukemia or leukosarcoma was made only after splenectomy in four instances *Hypersplenic* pancytopenia without evidence of leukemia in the peripheral blood or bone marrow is the usual preoperative status of patients in whom splenectomy reveals leukemia

The results are not to be interpreted as advocation of indiscriminate splenectomy in leukemia and leukosarcoma patients spleen removal is properly confined to a small number of especially selected cases

***Multiple Myeloma IV Abnormal Serum Components* and Bence Jones Protein** These serum increments are probably produced by abnormal plasma cells R Wayne Rundles Gerald R Cooper and Robert W Willett[8] (Duke Univ) studied *30 patients with multiple myeloma under therapy* and during relapse using electrophoresis and diffusion rates in the Tiselius apparatus and sedimentation analyses in the ultracentrifuge Abnormal components were recognizable in the electrophoretic *patterns of 25 patients In 17* the abnormal component migrated as gamma protein and in 8 between gamma and beta protein The chief abnormality associated with proliferating plasma cells seemed to be an unusually homogeneous serum globulin Two patients had two clearly abnormal constituents each

Range in quantity of abnormal plasma protein was 0 1 9 Gm./100 cc Some patients with little abnormal protein ex

(8) J Cl I 1 30 11 5 114 October 1951

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To explain the origin of Bence Jones protein the authors suggest that proliferating plasma cells produce protein of ab normal homogeneity and high molecular weight Bence Jones proteins are also abnormally homogeneous and their molecular weight is 1/3 1/6 that of the serum increments As plasma cell growth is suppressed by urethane abnormal serum pro tein and Bence Jones protein decrease and the latter may dis appear The opposite changes occur during relapse Thus Bence Jones proteins seem to be derived from serum incre ments as a fraction of the larger molecules they become filter able through the glomeruli The central phenomenon is ab normal plasma cell proliferation The protein abnormality varies from patient to patient but remains qualitatively con stant once it has developed

Bone Marrow Findings in a Case of Carcinomatosis Re semblance to Myelomatosis is reported by R M Hardisty[9] (Univ of Aarhus)

In a woman 49 with carcinoma of the breast blood studies showed red cells 2 580 000 hemoglobin content 9 Gm /100 cc white cells 3,200 myelocytes 1% metamyelocytes 1% polymorphonu clears 61% lymphocytes 23 per cent monocytes 13% plasma cells

(9) A ta m d d n 142 64 70 195

1% and platelets 330 000 X ray examination revealed numerous areas of destruction typical of metastatic deposits in nearly all the ribs many of the vertebrae and throughout the pelvic bones

Sternal puncture showed cellular marrow with normally active hemopoiesis but with an occasional clump of apparently syncytial cells with large oval deeply staining finely reticular nuclei and homogeneous blue cytoplasm These were considered metastatic neoplastic epithelial cells Marrow was aspirated from an iliac crest and examination of smears stained by May Grunwald Giemsa method revealed a strikingly different picture in that 54% of nucleated cells were large and oval, each with an eccentric deeply staining round nucleus whose chromatin was evenly dispersed in a reticular form and with a plentiful hazy blue cytoplasm sometimes containing small vacuoles Most of these cells were disrupted and in some the cytoplasm had almost completely disintegrated Some appeared to contain one or two small pale blue nucleoli and some showed a clear perinuclear *Hof* Although some of the cells were found in large clumps there was no suggestion of a syncytial arrangement The cells were remarkably uniform in size (approximately 20 μ) and structure No multinucleated cells or mitoses were seen Films showed practically no hemopoietic tissue and most of the remaining nucleated cells were mature polymorphonuclears and lymphocytes Sections prepared from some of the aspirated marrow fragments and stained with hematoxylin eosin revealed beyond doubt that the large cells were columnar epithelial cells from a well differentiated adenocarcinoma

In this case the diagnosis was never in doubt chiefly because of visible and palpable primary carcinoma However the case suggests a possible source of diagnostic error in instances of carcinomatosis of bones in which primary growth is less obvious and confusion with myeloma ' that is immature plasma cells could occur Carcinoma cells cannot be mistaken for mature plasma cells because of their larger size and the arrangement of their nuclear chromatin with its evenly dispersed closely woven reticular pattern and no apparent tendency to condense into large masses However they more closely resemble the less well differentiated cells found in the marrow in myelomatosis They are larger than mature plasma cells and their nuclear chromatin is less condensed and may be reticular with or without nucleoli virtually identical with the carcinoma cells described Only the widespread tendency of carcinoma cell cytoplasm to disintegrate might tend to distinguish them individually from such cells The case also illustrates value of bone marrow sections which settle diagnosis beyond doubt

Treatment of Multiple Myeloma with Urethane Experience with 66 Cases over 2½ Year Period is reported by William F Luttgens and Edwin D Bayrd[1] (Mayo Clinic and Found) The drug was at first given as a liquid solution containing 0 5 Gm /teaspoonful to be taken orally after meals diluted with a glass of water Later tablets containing 0 3 Gm urethane were used Initially 1 5 3 0 Gm in divided doses was given three times daily after meals daily dose was increased gradually by about 0 5 Gm increments every few days until the maximal amount tolerated had been reached Four patients received urethane intravenously only 4 Gm daily in 1 000 cc of 5% solution of dextrose in water to a total dosage of 24 68 Gm 7 received 40-100 Gm intravenously in addition to oral medication 13 patients unable to tolerate the drug stopped treatment before receiving an adequate amount Including the 7 patients given combined therapy 49 who received adequate therapy (100 Gm or more) or who died while under treatment were studied for survival time and subjective and objective improvement Degree of malignancy of the myeloma plasma cells obtained by bone marrow aspiration was estimated on that basis 48 urethane treated patients were compared with similarly studied controls who had received the customary treatment previously available ionizing irradiation or stilbamidine For groups graded III and IV total duration of illness of urethane treated patients exceeded that of the control group with most treated patients still alive when data were obtained and all controls dead Insufficient time has passed to allow conclusions concerning the patients in groups I and II in which duration of life of control patients is greater

About half the patients had definite relief from symptoms after urethane but only two were completely relieved Improvement was noted particularly in those with a milder form Only about a fifth of the patients showed objective improvement usually those having the less malignant disease Increase in hemoglobin concentration and decrease in erythrocyte sedimentation rate were the commonest objective signs of improvement There was no great change in serum proteins roentgen findings or percentage of myeloma cells in the bone marrow Bence Jones proteinuria did not disappear after treatment

(1) J A M A 147 824 8 7 Oct 27 1951

Leukopenia was noted in about 75% of patients at some time during therapy but no complications attributable to this occurred Thrombopenia and pancytopenia did not occur Anorexia nausea vomiting or diarrhea was observed in at least two thirds of patients Only rarely did a patient seem able to take 2 or 3 Gm daily regularly without difficulty 4 or 5 Gm daily was seldom possible even with treatment on alternate weeks Attempts to overcome this by having the patient dilute the drug well with water and take it immediately after eating or in tablet form were only partly successful

There was no essential difference in response of the small group given intravenous medication except for fewer gastrointestinal symptoms and prompter subjective improvement It is concluded that urethane is probably as good treatment as is at present available for multiple myeloma

PURPURAS

Demonstration of Thrombocytopenic Factor in Blood of Patients with Thrombocytopenic Purpura was done by William J Harrington Virginia Minnich James W Hollingsworth and Carl V Moore[2] (Washington Univ)

TECHNIC —Citrated blood or plasma from 10 patients with idiopathic thrombocytopenic purpura from 3 with secondary thrombocytopenia and from 7 nonthrombocytopenic subjects was given intravenously to healthy volunteers or patients with inoperable malignancies Platelets red and white cells were counted often during the following four hours and daily thereafter until control level were reached Bone marrow bleeding time capillary fragility silicone clotting time clot retraction and prothrombin consumption were studied in some patients

Blood or plasma from eight thrombocytopenic subjects regularly produced a prompt decrease in platelets in the recipients This was often apparent in 30 60 minutes becoming maximal in 2 3 hours and lasting 4-7 days (Fig 69) Blood from a patient with chronic lymphatic leukemia produced similar changes Transfusions from two thrombocytopenic patients another patient with chronic lymphatic leukemia and a child with hypoplastic anemia gave negative results These were verified by second observations in two cases

(2) J Lab & Clin Med 38 1 10 July 1951

If life span of platelets is four to seven days then the thrombocytopenia induced was apparently due to rapid disappearance of platelets from the blood and not to inhibition of formation Furthermore the entire clinical and laboratory syndrome of thrombocytopenic purpura was induced in two recipients within the first few hours it persisted for four to seven days paralleling duration of the low platelet count

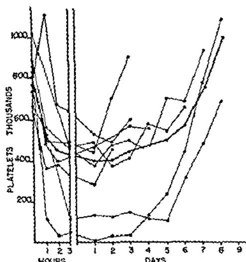


Fig 69—Th mbocyt p ff t p od d by t f g 500 t e d wh l blood t pl m q l t f m ght p ti t w th th mbocyt p c pu pu T f w g t 0 tim M ff t p se t d by b vy l (C t y f Ha gt W J t l J Lab & Cl n M d 38 1 10 J ly 1951)

When the platelet reduction was greatest bleeding time was prolonged and prothrombin consumption abnormally low Bone marrow megakaryocytes showed characteristic immaturity during the thrombocytopenic period Studies on survival of transfused platelets have indicated that platelets disappear rapidly in patients with idiopathic thrombocytopenic purpura

Plasma obtained from two donor patients after platelet levels had returned to normal following splenectomy caused approximately the same degree of thrombocytopenia in recipients as it had before splenectomy Also transfusion of

thrombocytopenic plasma into a patient whose spleen had been removed during gastrectomy for carcinoma of the stomach caused a definite drop in platelet count

Coincident with administration of cortisone to a patient with thrombocytopenia who after splenectomy failed to re spond to both ACTH and cortisone platelets increased to over 1 000 000/cu mm and plasma lost its ability to produce thrombocytopenia

Initial studies on the nature of the thrombocytopenic fac tor have shown that it is a plasma constituent present in the globulin fraction and that it is stable in acid citrate dextrose solution for at least nine days at — 5 + 5 and + 25 C

[This article a classic contribution to clinical investigation clearly indicates the presence of a thrombocytopenic factor *not* of splenic origin in the plasma of at least certain patients It vastly increases the weight of evidence favoring increased destruction of platelets as a cause of idiopathic thrombocytopenias —Ed]

Studies on Platelets II Effect of Transfusions of Plate let Rich Polycythemic Blood on Platelets and Hemostatic Function in "Idiopathic" and "Secondary" Thrombocytopenic Purpura Thrombopenias are of two general types the idio pathic characterized by abundant megakaryocytes in the marrow and the secondary with marrow infiltration by pathologic cells (leukemia) or marrow hypoplasia or aplasia with resultant reduced platelet formation Idiopathic thrombo penia may be acute or chronic Abundance of megakaryocytes in this form suggests an unknown mechanism extrinsic to the marrow of platelet depression

Since other methods for determining platelet survival have too many sources of error Mario Stefanini Jyoti B Chat terjea William Dameshek Leda Zannos and Enrique Perez Santiago[3] (Tufts College) used the multiple silicone coated syringe technic to transfuse platelet rich polycythemic blood modifying the procedure only by advance transfusion of fresh blood to reduce possible platelet hunger of tissues Of 22 patients studied 12 had acute idiopathic thrombocytopenic purpura 2 had the chronic variety and 8 thrombocytopenia due to primary bone marrow disease Calculations of the rate of disappearance of transfused platelets in patients permit their classification into two well defined main groups of

(3) ood 7 53 76 J ary 195

thrombopenia Disappearance rate was high in the idiopathic group and in one of the two patients with the chronic type and low platelet count In the other with a higher platelet count the platelets survived for 24 hours However original platelet level was generally reached in one half to three hours after transfusion In two patients platelet transfusion was repeated some time after unsuccessful splenectomy platelet count after the second transfusion was identical in course to that after the transfusion before surgery In eight secondary thrombopenia patients disappearance was not complete for at least 24 hours in most not for 48 72 hours and in one not for 96 hours Behavior of clot retraction and prothrombin activity of serum paralleled closely that of platelet count Bleeding time and capillary fragility remained improved in most for 24 48 hours after platelet count had returned to initial level and in every instance hemorrhagic manifesta tions also were improved In keeping with previous findings there were two instances of sustained or permanent remission In both the injected platelets disappeared promptly from the circulation but within 24 hours platelet count began to rise suggesting that polycythemic blood might contain a stimula tory principle which could influence or accelerate a spontane ous remission

These observations make it evident that rate of disappear ance of platelets from the circulation is closely related to the basic process responsible for the deficiency The mechanism responsible for the sudden drop in platelets in acute idio pathic thrombocytopenia is still obscure According to one theory idiopathic thrombocytopenic purpura is a form of hypersplenism the spleen through mediation of undeter mined humoral factors inhibits production and possibly delivery of platelets from megakaryocytes Another theory suggests that a splenic factor might alter capillary endothe lium and also reduce platelet production [However it has re cently been reported that the intravenous administration of citrated plasma from patients with thrombocytopenic purpura both before and after splenectomy causes a rapid drop of platelets in normal subjects (see preceding article) —Ed] The problem is complicated by lack of uniform response to splenectomy and by history of allergic manifestations in a

thrombocytopenic plasma into a patient whose spleen had been removed during gastrectomy for carcinoma of the stomach caused a definite drop in platelet count

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(3) Blood 7 53 76 January 1952

splenic pulp and in a peripheral vein in three patients with thrombopenic purpura and in one with carcinoma of the kidney Aft r correction for hematocrit differences these are for pulp (corrected) and peripheral vein re pectively in thousand /cu mm 21 50 8.24 170 1? 113 7 20? 80 161.25 and 1 3?3 4 1 0?6 4 Unle s indicating local production the higher value in the splenic pulp are consistent with sequestration —Ed.]

Transfusion of Human Blood Platelets With Note on Transfusion of Granulocytes Utilizing multiple silicone coated syringes in direct transfer of platelet rich polycythemic or normal blood into patients with various thrombopenic states 42 transfusions were given 23 patients by Erwin O Hirsch and Frank H Gardner[5] (Harvard Med School) With approximately 500 cc /transfusion only one failed to raise platelet count significantly 20 100% of platelets were recovered in recipients who manifested rises as high as 130 000/cc Highest yields and longest platelet survivals (five to six days) were noted in aplastic anemia (Fig 70) acute leukemia and pancytopenia with normal bone marrow It is assumed that in aplastic anemia failure of platelet formation is the only cause of thrombopenia therefore the life span of transfused platelets would represent normal life span of platelets The life span of five to six days thus ascertained agrees favorably with other results Platelet recovery and survival rates were lowest in acute thrombopenia suggesting rapid platelet destruction by a plasma factor In chronic idiopathic thrombopenia platelet life span was intermediate suggesting slower destruction Presence or absence of spleen did not alter results in acute or chronic thrombopenia In four patients with massive splenomegaly platelet survival was very short In cases of this type no evidence of a platelet destroying plasma factor which might confirm the concept of sequestration by the spleen has been found Data are still insufficient to evaluate presence or absence of naturally occurring platelet antibodies of the type seen in the human A B O system but progressively decreased platelet survival in two of three patients after repeated direct transfusions suggests that platelet destruction may result from repeated direct transfusions

Blood oozing stopped dramatically in all but the one patient whose platelet count failed to rise When transfused platelets remained in the circulation for at least four days no new petechiae or ecchymoses appeared during the life span of

(5) J L h & Cl M 1 39 556 569 Ap 1 195

number of instances of idiopathic thrombocytopenia It must be concluded that this disease is protean and caused by various pathogenic mechanisms

These studies on rate of platelet disappearance seem to indicate that a destructive mechanism acts against circulating platelets at least in the acute disease the same destructive mechanism might conceivably affect platelets at the periphery of megakaryocytes or inhibit their production completely In any event use of fresh directly transfused polycythemic blood especially when nonwettable surfaces are used appears to be of definite therapeutic value

Studies on Platelets III Absence of "Selective Sequestration" and Destruction of Platelets by Spleen in "Idiopathic" Thrombocytopenic Purpura (I T P) was investigated by Mario Stefanini Jyoti B Chatterjea William Dameshek C Stuart Welch and Orvar Swenson[4] (Tufts College) by means of direct experiments at operation No significant differences in platelet number or function could be found in samples of blood collected from the splenic artery and vein in patients with I T P or other pathologic conditions In two cases of I T P splenic pulp blood and blood from the peripheral circulation showed a comparable number of platelets in respect to the various hematocrit readings The injection of platelet rich blood in the peripheral circulation failed to establish a difference in platelet count between blood from the splenic artery and from the splenic vein No significant diminution of the number of platelets in the splenic vein blood followed the direct injection of platelet rich blood in the splenic artery A similar result was observed in one case of hereditary spherocytosis in which the spleen admittedly does not sequester platelets These various experiments failed to indicate any selective sequestration of platelets by the spleen in idiopathic thrombocytopenic purpura

[Yet as stated by the authors the lack of differences in the platelet count between splenic arterial and venous blood does not therefore eliminate the possibility that sequestration may take place periodically in the organ In other words positive findings would have been significant negative findings are not necessarily so especially perhaps under the artificial conditions of anesthesia and operation Moreover despite other statements in explanation of a lack of significance owing to inherent errors in platelet counting and some degree of hemoconcentration, it is interesting to compare the authors figures for platelet counts in the

(4) Blood 7 89 301 M h 1952

tendency The excellent correlation between platelet survival and length of improvement suggests that improvement of the hemorrhagic state was due to transfused platelets and not to some other factor in the transfused blood Moreover several of the patients had failed to respond to fresh bank blood (un der 12 hours old) and to serum

"**Idiopathic Thrombocytopenia Review of 89 Cases with Particular Reference to Differentiation and Treatment of Acute (Self Limited) and Chronic Types** is presented by Erwin O Hirsch and William Dameshek[6] (New England Center Hosp Boston) This report supports the views that at least two different clinical entities are included in the terms idio pathic thrombocytopenic purpura Werlhof s disease and essential or primary thrombocytopenia and that the symptom of purpura is not an essential part of these entities The series includes 26 acute self limited cases of which 18 were proved by follow up 55 chronic cases of which 52 were proved and 8 unclassified cases

The acute type was sudden in onset with a short course low mortality (1 death among 23 patients treated conserva tively) and complete recovery of platelet count in a few months Purpura was usually present The disease was sometimes preceded by a nonbacterial infection Sometimes it seemed to represent an allergic reaction to a chemical drug or other type of allergen but no etiologic factor could be found in about half the cases Eosinophilia and lymphocytosis were about as frequent in the idiopathic as the postinfectious and allergic types Repeated attacks were rare except when the disease resulted from true allergy with re exposure as in quinidine or sedormid® purpura

Onset of the chronic variety was usually insidious but once established the disease was generally permanent even though clinical remissions were the rule During these signifi cant thrombocytopenia persisted and most patients continued to show mild bleeding signs All but three patients gave his tories of easy bruising menorrhagia or local bleeding Eti ologic factors such as those seen in the acute type were rare In children both sexes were equally affected but a high inci dence in girls and women especially in the second decade suggests that the development of the adult female hormone

(6) A M A A h I t M d 88 701 728 Decembe 1951

Fig 70—R lt of repe t d pl t l t tr n fu n pl t c an m l theo t al pl t l t co nt sol d d t lse d t l t l t nt Th fi t t n f w t hn ally un t f tory y ld f th nd nd th d d d n t d ff lth gh b f th th d t n f n p t t d d not f v th mbocyt pe Lf p f pl t l t wa x t f n d y o g n lly (hl d f) bu p t d t a f w d ly ff (Co y f Hi h F O sed C n F H J Lab & Cl Med 39 556 569 Ap l 19 2)

transfused platelets With platelet survivals of less than one day this could not be evaluated Whereas bleeding from needle punctures and the genitourinary tract is usually controlled beyond the life span of transfused platelets oozing from gums and fresh petechiae and ecchymoses usually reappear The fact that direct transfusions favorably affected bleeding in thrombopenic patients suggests that bleeding was not primarily due to vascular difficulty or circulating anticoagulant although such factors might aggravate an already existing bleeding

Splenectomy cures about two third of the patients with chronic idiopathic thrombocytopenic purpura Because of low operative mortality in the absence of purpura and the possibility of future hemorrhagic crises the operation should be done as soon as the diagnosis is made in patients free from purpura It is probably of no value in the thrombocytopathic form of the disease

Idiopathic Thrombocytopenic Purpura in Childhood William A Newton Jr and Wolf W Zuelzer[7] (Wayne Univ) stress differences in the condition in children compared to adults Diagnostic criteria included under 100 000 platelets coupled with abnormal bleeding tendency prolonged bleeding time delayed incomplete or ab ent clot retraction and/or increased capillary permeability Diagnosis was confirmed by bone marrow aspiration in 30 of the authors 47 cases

Ages ranged from 9 days to 11 years average 5 3 years Ratio of boys to girls was 1 4 1 in contrast to female predominance among adults Twenty two had had no antecedent infection and many of the others had had only trivial illness Measles had preceded purpura 5 days to 5 weeks in six patients Nine had had some form of allergy including hives in six asthma in two and infantile eczema in one Only one child had a family history of impressive bleeding

Hepatomegaly and splenomegaly were found only once although the tip of the spleen was palpable in five Petechial hemorrhages and ecchymoses occurred in all but one case and were combined with mucosal bleeding in 21 Central nervous system bleeding was found in four patients two of whom died Autopsy revealed multiple petechial pericapillary hemorrhages related to acute necrotizing vasculitis and resembling hemorrhagic encephalitis which follows arsenic treatment

Platelets were always fewer than 60 000 and ordinarily virtually absent bleeding time was invariably prolonged but clotting time was normal in 42 children and slightly prolonged in 1 Clot retraction was abnormal in 23 of 29 but was complete in 48 hours in 6 Capillary permeability was increased in 23 of 32 patients Anemia below 10 Gm was encountered in 25% and was severe in half of these Although 30% had lymphocytosis no instance of leukopenia was found Megakaryocytes in bone marrow were increased in 11 normal in 4 and

(7) New England J Med 245 879 885 Dec 6 1951

pattern predisposes to the disease Occasional familial incidence suggests some constitutional predisposing factor but the disease is not congenital

The importance of recognizing the two separate forms of the disease is mainly prognostic and therapeutic Because of the self limited course in acute thrombocytopenia ACTH and cortisone therapy cannot be properly evaluated In chronic cases success of a procedure such as splenectomy is established only if thrombocytopenia present at least four months is followed by a sustained rise of platelets to normal for more than four months

Diagnosis can usually be made by inspection of stand cover slip smears except in mild cases in which a platelet count may be valuable The tourniquet test bleeding time clot retraction and prothrombin consumption test of Quick may be confirmatory Once diagnosis is confirmed a marrow preparation is the best means of finding whether thrombocytopenia is due to lack of megakaryocytes or exists despite their normal number One megakaryocyte per low power field in a cellular bone marrow smear suggests that lack of thrombocyte precursors is not the cause If splenomegaly is present such known causes of enlargement as rheumatoid arthritis liver disease lymphoma and disseminated lupus must be ruled out

In distinguishing between acute and chronic idiopath thrombocytopenia no single criterion is infallible In the authors experience acute onset and negative past history were rare in chronic and frequent in acute cases Slight splenic enlargement is occasionally seen in chronic but not in acute types If criteria are contradictory frequent observations and platelet counts for four to six months will usually give the answer Persistence of thrombocytopenia even if symptoms disappear indicates chronic disease

Supportive measures particularly transfusion of fresh blood and splenectomy are the most important available therapeutic procedures Decision regarding splenectomy is difficult during an attack of acute purpura splenectomy was not found to be convincingly effective and supportive measures should be used Elective splenectomy should be done only after frank purpura has subsided as otherwise it carries an undue mortality

ment in adults and children in several large series compiled from the literature Viewed against the background of the natural course of the disease successful results in children cannot be attributed to early splenectomy as spontaneous recovery is the rule In children splenectomy should probably be reserved for instances of uncontrollable bleeding and chronic recurrent purpura

Role of Complement in Sedormid® Purpura, which is characterized by rapid development of thrombocytopenia and increased capillary fragility when the drug is taken by a sensitized individual is discussed by J F Ackroyd[8] on the basis of detailed study of three such cases

Addition of normal human complement to platelet rich plasma from patients recovered from sedormid® purpura was found to increase platelet lysis in presence of sedormid® The drug also caused lysis of normal platelets when with added complement these were suspended in plasma from a sedormid® sensitive patient but the same patient s platelets when suspended in normal plasma to which complement had been added did not undergo lysis in the presence of sedormid®

Complement was fixed when blood from sedormid® sensitive patients was allowed to clot in the presence of the drug but was not fixed by sedormid® in the blood of normal controls If normal platelets were suspended in sera of patients recovered from sedormid® purpura and sedormid® was added complement was fixed and platelets underwent lysis Without complement sedormid® caused platelet agglutination but complement was required before lysis occurred Sedormid® caused neither lysis of platelets nor fixation of complement when added to normal serums in which platelets of sedormid® sensitive patients had been suspended It was therefore concluded that platelet lysis in the blood of patients recovered from sedormid® purpura was due to action of a plasma factor and not to any platelet abnormality

Complement fixation by sedormid® depends on four factors sedormid® complement serum from a sensitized patient and platelets it does not occur when any one is absent No other immunologic lytic phenomenon has been described in which more than three interacting factors are involved antigen antibody and complement In this reaction guinea pig

(8) Clin S 10 185 207 May 1951

decreased in 8 instances the specimen was unsatisfactory in 7

Blood transfusions, given to 27 patients for anemia or continued blood loss restored hemoglobin content but did not affect the underlying condition Splenectomy was performed in seven patients Bleeding subsided in 29 of 42 patients within a month but in 6 it continued over six months and in 1 for three years All bleeding in the last patient stopped after splenectomy but platelet count showed only a transitory rise Spontaneous recovery was characterized by cessation of bleeding

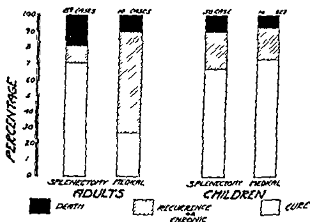


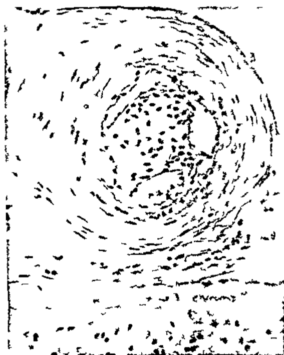
Fig 71 —Re ults of d opath pu pura tr atme t d lts and ch ld n (Cou t y of Newt n W A J d Zu l e W W N w E gla d J Med 24 8 9 885 Dec 6 1951)

with return to normal of capillary fragility followed in most instances by gradual rise in platelet count and return to normal bleeding and clot retraction time

Of 40 patients treated conservatively 2 died of hemorrhagic encephalitis within a few days of onset Of 38 survivors 35 were followed at least 6 months when 32 had had no recurrence purpura recurred in the other 3 at intervals of 4 18 months Ordinarily it appears to be a short disease in children with recurrence and spontaneous subsidence even after recurrence After splenectomy platelet count rose immediately bleeding stopped and there was no recurrence in three of six children but the operation was a partial or total failure in the other three

Figure 71 compares results of thrombopenic purpura treat

cular occlusion involving nearly every tissue In some in stances the occlusive material was eosinophilic amorphous finely granular and covered with endothelial cells Serial sec tions often showed it to be continuous with similar material located subendothelially Some thrombi contained numerous small mononuclear cells but collagen formation was not seen



F g 72—Il led oc l tmen geal rteri l d ed from × 255 (Cou y f M h m G C t l Blood 6 706-719 A gu t 1951)

The normal structure of the vessel wall was often absent at these sites with pronounced thinning of the walls dilatation of the vessel and formation of occluded aneurysms Inflam matory reaction was not associated with the lesions (Fig 72)

There was little doubt that in one patient the course lasted at least three years since re examination of the spleen re moved three years before death revealed characteristic lesions

complement can replace human complement but red and white cells cannot replace platelets

Sedormid® probably unites chemically with platelets to make an antigen and thrombocytopenia results from lysis of this platelet sedormid® antigen by antibody and complement Since platelets of normal and sedormid® sensitive patients undergo lysis in vitro the antigen is probably formed whenever sedormid® contacts platelets and therefore must be produced in all individuals taking the drug

The probability that this antigen only slightly stimulates antibody formation explains why only a few of those taking the drug manufacture the antibody and so develop thrombocytopenia It is suggested that sedormid® also unites chemically with the capillary endothelium which then reacts with the same antibody causing increased capillary permeability

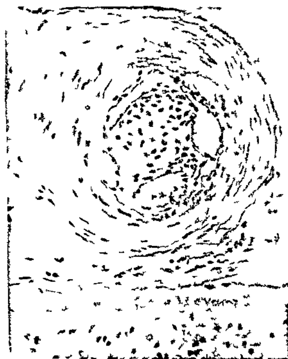
Thrombotic Thrombocytopenic Purpura, Disseminated Disease of Arterioles This syndrome in characterized by widely disseminated hyalin thrombi in the terminal arterioles and capillaries of many organs Clinically there are acute onset fever hemolytic anemia thrombocytopenic purpura and bizarre mental and neurologic manifestations which result from arteriolar occlusion Hemolytic anemia thrombocytopenic purpura and signs of occlusion of small arterioles do not occur together in any other clinical entity The course is almost always progressive and fatal Although commoner in females the disorder has been found in persons of both sexes and of all ages

Gordon C Meacham J Lowell Orbison Robert W Heinle Howard J Steele and J Alpert Schaefer[9] (Western Reserve Univ) discuss two patients one of whom had a significant remission after splenectomy Abnormal agglutinins in the blood and a positive result of the Coombs test were not noted in contrast to other types of acquired hemolytic anemia Spherocytosis was occasionally present Histologic observations supported the concept that the degenerative lesion of vessels is primary and similar to that in so called collagen diseases There is no conclusive proof that the vascular thrombi are composed of platelets but rather appear to represent intramural degeneration

The significant microscopic finding in these cases was vas

(9) Blood 6 706 719 August, 1951

cular occlusion involving nearly every tissue In some in stances the occlusive material was eosinophilic amorphous finely granular and covered with endothelial cells Serial sec tions often showed it to be continuous with similar material located subendothelially Some thrombi contained numerous small mononuclear cells but collagen formation was not seen



Fg 7 —H l d oc l m g l te l d d f m × 55 (C t y f M h m G C t l Bl d 6 706 719 A g t 1951)

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The probability that this antigen only slightly stimulates antibody formation explains why only a few of those taking the drug manufacture the antibody and so develop thrombocytopenia It is suggested that sedormid® also unites chemically with the capillary endothelium which then reacts with the same antibody causing increased capillary permeability

Thrombotic Thrombocytopenic Purpura, Disseminated Disease of Arterioles This syndrome in characterized by widely disseminated hyalin thrombi in the terminal arterioles and capillaries of many organs Clinically there are acute onset fever hemolytic anemia thrombocytopenic purpura and bizarre mental and neurologic manifestations which result from arteriolar occlusion Hemolytic anemia thrombocytopenic purpura and signs of occlusion of small arterioles do not occur together in any other clinical entity The course is almost always progressive and fatal Although commoner in females the disorder has been found in persons of both sexes and of all ages

Gordon C Meacham J Lowell Orbison Robert W Heinle Howard J Steele and J Alpert Schaefer[9] (Western Reserve Univ) discuss two patients one of whom had a significant remission after splenectomy Abnormal agglutinins in the blood and a positive result of the Coombs test were not noted in contrast to other types of acquired hemolytic anemia Spherocytosis was occasionally present Histologic observations supported the concept that the degenerative lesion of vessels is primary and similar to that in so called collagen diseases There is no conclusive proof that the vascular thrombi are composed of platelets but rather appear to represent intramural degeneration

The significant microscopic finding in these cases was vas

(9) Blood 6 706-719 Aug 1951

noses The albumin fractions are normal and unchanging Cryoglobulins are absent Perhaps the main condition to be differentiated from this syndrome is myeloma with hemor rhagic manifestations Many means of differentiation are available such as the typical marrow presence of cryoglobu lins and mucous membrane bleeding in myeloma which do not occur in the described syndrome With regard to the patho logic physiology of this type of purpura nothing definite can be said

Investigations of Constitutional Thrombopathy (Wille brand Jurgens) on Åland Islands were carried out by R Jurgens (Basel) and H Forsius (Helsingfors) in 1949 50 The material comprised five family groups in which heredi tary hemorrhagic diathesis due to constitutional thrombopathy had been described in 1932 by von Willebrand and Jurgens

Among 200 persons investigated 26 were found to be bleeders with skin and mucosal bleeding muscle hematomas and genital joint retinal and conjunctival bleeding Accord ing to Federly and Lenz the constitutional thrombopathy is transmitted by a single dominant gene

Bleeding time in some was greatly prolonged pinching Rumpel Leede and capillary resistance tests gave positive re sults Platelets never numbered less than 350 000 number of megakaryocytes was normal The former were partly abnor mally large containing vacuoles sometimes showing scarcity of granules sometimes granulopyknosis The megakaryo cytes also showed scarcity of granules

The prothrombin consumption test (Quick) gave positive results in several cases recalcification time was often pro longed

Testing of the elasticity of the thrombi (Hartert) showed a notably decreased elasticity developmental time of the thrombi was prolonged

The pathogenesis of the bleeding in constitutional throm bopathy depends on disturbances of the blood vessels de creased ability of the platelets to agglutinate and accord ingly disturbances in the first phase of the clotting process due to lack of a platelet enzyme which acts on the thrombo plastinogen

(2) Schw m d W h sch 81 1248 1253 D 15 1951

identical with those found at autopsy in other organs After splenectomy the anemia was much improved and the patient was in remission for 28 months although hypertension developed during that time Splenectomy has been done in similar patients only three times with death occurring in each before the therapeutic effect could be judged This patient also improved during the first 10 days of ACTH therapy with subsequent severe relapse while the drug was continued Only 20 mg a day was given larger doses might have been more effective However the problem then arises whether vigorous hormone therapy might have caused rapid healing and fibrous obliteration of affected vessels as has been noted in patients with polyarteritis nodosa treated with cortisone

The authors propose that the term thrombotic thrombocytopenic purpura be retained until better understanding of the pathologic physiology of the condition permits application of a more suitable name

Three New Cases of Purpura Hyperglobulinemia Study in Long Lasting Benign Increase in Serum Globulin Since Jan Waldenstrom[1] (Univ of Lund) first described it in 1943 the syndrome of unexplained relapsing chronic purpura associated with a usually unexplained hyperglobulinemia particularly due to increase in gamma globulin has been reported by several European authors

The purpura occur chiefly on the legs and mainly after exertion There are no other signs of a hemorrhagic disorder although mild normochromic anemia or leukopenia may be present The lesions disappear rapidly but characteristically leave behind pigmented spots The liver and spleen are usually of normal size but some lymphadenopathy is common The hyperglobulinemia can usually be traced back many years and there is no tendency for it to increase or disappear Erythrocyte sedimentation rate is increased due to the elevated globulin level No known clinical entity can be utilized to encompass these cases A virus etiology is suggested by the fact that the electrophoretic pattern of the gamma globulin peak from serums of these patients resembles that obtained from lymphogranuloma serums with an elevated globulin content However this pattern is also found in cirrhosis and collage

(1) A ta m d s a d a 14 931 946 195

ley Miller and William H Bullock[4] (Ann Arbor Mich) treated 10 patients In none was a specific cause found They were aged 3 60 and eight were female All were in an active stage when therapy was begun but none were in acute hemor rhagic crisis Platelet levels ranged from less than 1 000 to 10 800/cu mm Pretreatment marrow studies uniformly re vealed normal erythro and granulopoiesis with numerous megakaryocytes which showed little or no platelet budding ACTH or cortisone was given parenterally for 8 28 days depending on the response ACTH was given every six hours for a total of 100 mg a day except in one patient who re ceived 160 mg for five days Treatment was terminated by daily decrements of 25 mg Cortisone was given in two doses daily for a total of 100 300 mg

The usual platelet response was an abrupt and progressive rise which developed within a few days On discontinuance of therapy there was a sharp decline which in favorable cases was not to pretreatment levels Subsequently the platelets usually increased and the rise continued for many months All patients showed clinical improvement with decreased capillary fragility even those with a poor platelet response Serial bone marrow examinations revealed close correlations between the numbers of megakaryocytes showing platelet budding and the levels of circulating platelets Complete clin ical and hematologic remissions lasting up to the time of reporting were seen in three patients including those who had not responded to splenectomy One patient relapsed com pletely but subsequent splenectomy was successful An other responded to hormone therapy clinically and after sub sequent splenectomy had a sustained hematologic and clinical remission

The authors concluded that although the course of this disease is variable and spontaneous remissions occur ACTH or cortisone therapy may induce remissions Even though the effects may be temporary the operative risk attending splenec tomy is lessened by such treatment

Effect of Corticotrophin on Chronic Severe Primary Thrombocytopenic Purpura is reported by Robert S Evans and Chi Kong Liu[5] (Stanford Univ)

(4) T A Am Ph 64 199 03 1951
(5) A M A A h I t M d 88 503 506 O t b 1951

Treatment of the bleeding consists of repeated transfusions of blood or plasma Locally a thrombin preparation should be used

Splenectomy for Fulminating Episode of Essential Thrombocytopenic Purpura is reported by Albert P Giannini[3] (Canton O) in nine patients seen over five years All showed the typical signs of the disease increased capillary fragility diminution of circulating thrombocytes delayed clot retraction hemorrhagic episodes with generalized petechiae plus ecchymoses in various tissues All underwent splenectomy in the acute fulminating phase None died

Patients age range was 13 67 years There were twice as many females Fresh whole blood transfusions were used freely in all patients Bleeding time was prolonged in five but all showed a delayed or absent clot retraction Five patients preoperatively had pain in thighs and back Four had mild peripheral eosinophilia In two the spleen was palpable Three had accessory spleens Medical measures were unsuccessful before operation

All patients ultimately showed return to a nearly normal platelet count postoperatively There were two recurrences one probably due to generalized reticuloendothelial hyperplasia the other of unknown cause Usually the platelet count began to increase a day or two after splenectomy rising at the rate of 5 000 100 000/day Bone marrow studies in the patients were within normal limits and had a normal number of megakaryocytes The spleen showed such nonspecific changes as perisplenitis hyalinization of the septa and capsule reticuloendothelial hyperplasia congestion of the splenic sinuses and increased eosinophils in the splenic pulp

Total white cell count consistently rose temporarily after operation to between 20 000 and 30 000 Good clinical results were obtained even without a postoperative rise in platelets to normal Splenectomy proved lifesaving in these cases all but two patients had no recurrences

¶ The next three articles illustrate the great value in many patients of ACTH or cortisone in improving vascular competence with or without increase in platelet levels —Ed

Effects of ACTH and Cortisone on Idiopathic Thrombocytopenic Purpura Frank H Bethell Muriel C Meyers Stan

(3) S g Gy c & Ob t 94 2 9 238 F b y 195

CASE 1—Woman 59 with idiopathic thrombopenic purpura of several years duration was hospitalized in March 1945 Because of increasing purpura splenectomy was performed Improvement was striking Purpura recurred in 1950 after administration of various drugs and increased despite their discontinuance The only abnormality of blood constituents was a platelet count of 25 000/cu mm Bone marrow studies revealed an abundance of megakaryocytes without evidence of platelet formation She was given 100 mg ACTH (Armour) intramuscularly daily for five days followed by 25 mg daily for five days Platelet response exhibited a peak of 580 000 on the fifth day of treatment On the ninth day repeat marrow studies showed abundant platelets at the periphery of the megakaryocytes She was discharged on 25 mg ACTH intramuscularly every other day However two days after discharge an upper respiratory infection and pain in the left knee developed and she resumed ingestion of aspirin Purpura reappeared a few hours later Eight days later platelet count was 21 000 ACTH therapy was resumed 100 mg intramuscularly daily with a prompt rise in platelets This dose was maintained for nine days followed by 50 mg daily for four On the 13th day of treatment platelet count reached 2 000 000 and the medication was omitted The 49th day after cessation of treatment it had receded to 200 000 A week later it dropped to purpuric levels and remained at low levels

CASE 2—Man 43 first noted purpura in 1943 For the next five years he had intermittent ecchymoses nosebleeds and hemoptysis In 1948 platelet count was 30 000 Splenectomy was performed with prompt rise of platelets to over 100 000 and cessation of bleeding In December 1949 purpura recurred In 1951 platelet count was 20 000 and he had symptoms of bleeding ACTH 25 mg given intramuscularly every six hours for two days produced a ri e in platelets Two days later he was discharged on 25 mg ACTH daily but was reho pitalized after four days with a platelet count of 50 000 Cortisone 100 mg taken orally every eight hours caused a rise of platelets to 1 000 000 on the fourth day of treatment Over the following week with corti one dosage being gradually decreased to 50 mg daily platelet count fell to 27 000 The seventh day after cessation of treatment he was asymptomatic platelet count was 14 000 and remained at purpuric levels

CASE 3—Man 32 with purpura for seven years was hospitalized Platelets numbered 59 000 and megakaryocytes without platelet formation were present in marrow aspirate in normal numbers Cortisone 300 mg orally daily was administered There was a sharp rise in the platelet level to 410 000 on the fourth day of treatment Cortisone therapy was omitted and splenectomy performed Platelet count continued to rise in the usual fa hion ascending to about 2 000 000 on the third postoperative day

These cases indicate that in both presence and absence of the spleen platelet formation in idiopathic thrombopenic purpura can be stimulated by administration of ACTH or corti

Woman 41 complained of spontaneous bruising small skin hemorrhages bleeding gums and frequent nosebleeds since age 35 On initial hospitalization at 37 for continuing complaints large ecchymoses over the body and petechiae of the lower legs and ankles were found Blood picture was normal except for persistent platelet counts approximating 10 000 and normal to increased mega karyocytes in the bone marrow Bleeding time was 12 m n es clotting time normal and there was no clot retraction

The spleen weighing *206 Gm* was removed at that time and was found normal histologically Postoperative platelet count was 200 000 with remission of signs for one month after which the syndrome recurred with platelets again numbering 10 000 30 000 Eighteen months after splenectomy hysterectomy was done to con trol excessive menstrual bleeding Bleeding tendency continued and she began to complain of chronic fatigue

One year later ACTH therapy was begun with 25 mg every four hours for three weeks then 25 mg daily for two weeks On the fifth day the petechiae faded platelets had increased by the seventh day when spontaneous bleeding ceased and capillary fragil ity became normal Bleeding time fell to normal during the second week Platelet count rose to 140 000 before ACTH dosage was r duced then dropped to 40 000

Symptom free for two months the patient gradually relapsed thereafter Four months after the first course ACTH was again started with 25 mg daily for two weeks without effect She was then hospitalized and given doses above 150 mg a day Response was sluggish compared to the first course but was clinically as adequate After that 25 mg was given daily during alternate two week periods and she remained symptom free for three months

The authors consider that the unequivocal clinical and hematologic response seen twice in this patient indicates that a mechanism fundamental to the cause of primary thrombo cytopenic purpura was modified by ACTH No accessory spleen had been found during hysterectomy it is therefore believed obvious that the spleen and accessory splenic tissue were not responsible for depressing formation of or destroy ing thrombocytes by hypersequestration and phagocytosis Continued disease activity seemed due to production of suf ficient platelet destroying protein by tissues other than the spleen An analogous situation is often seen in acquired hemo lytic anemia after splenectomy

Effects of ACTH and of Cortisone on Platelets in Idio pathic Thrombopenic Purpura Bernard M Jacobson (Harvard Med School) and William D Sohier[6] (Massachusetts Gen l Hosp) report three cases

(6) N w Engl d J Med 246 247 249 F b 14 195

by inversion A paraffined stopper or tissue is used to close the tube After 15 minutes at 37 C the clot is loosened and after 10 more minutes the clotted blood is centrifuged The serum prothrombin time is determined 15 and 60 minutes after centrifugation

The values for clotting time of serum from hemophilic blood obtained by this new technic (method 2) range from 8 to 13 seconds when determined by method 1 Normal blood values range from 15 to 120 seconds as do those for thrombocytopenic blood because the platelet factor is added in method 2 Hence hemophilia can be readily differentiated from thrombocytopenia or thrombasthenia By means of this test a positive diagnosis was made in each of more than 25 hemophiliacs The test is of particular value for patients who have only slightly prolonged or even normal clotting time a negative family history and a bleeding tendency so mild as to manifest itself only after operations such as tonsillectomy or tooth extraction or after severe trauma The conventional diagnostic triad of bleeding tendency prolonged clotting time and hereditary pattern is not always available nor is it always specific for hemophilia as in congenital hypoprothrombinemia The new test appears to be specific

Variations in clotting time in serial studies on a single patient are attributed to inevitable slight variations in technic The authors believe that the inborn defect in hemophilia is quantitatively constant After standardization of the prothrombin consumption test it was found that serial values were fixed This test has also made possible the determination of variations in affected members of a given family Five families were studied with bleeding tendencies varying from extremely mild to severe It was found that all of the affected members of one family were similar both clinically and in regard to the clotting factors in their blood In other studies sons of known carriers who were normal at birth have remained free from bleeding tendency and have maintained normal prothrombin consumption On the other hand affected children cannot outgrow a disease such as hemophilia or congenital hypoprothrombinemia There is evidence that a carrier not only transmits the clotting defect but also the degree of defect Changes in bleeding tendency are probably induced by secondary factors superimposed on the basic deficiency

sone Either hormone may be useful in preparing the patient for splenectomy If splenectomy is not indicated or has already been performed either may tide the patient over a critical bleeding episode

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COAGULATION DEFECTS

Hemophilia Clinical and Laboratory Observations Relative to Diagnosis and Inheritance The basic coagulation defect in hemophilia according to Armand J Quick and Clara V Hussey[7] (Marquette Univ) is now fairly convincingly established as a lack of thromboplastinogen This is one of five factors indispensable for the formation of thrombin The others are prothrombin calcium labile factor and a platelet constituent The prothrombin consumption test is the only available method for estimating the thromboplastin activity of blood it is hence important in the study of hemophilia

METHOD 1—The test is based on determination of prothrombin remaining after blood has been clotted Three samples of 2 cc. blood are clotted in separate tubes and centrifuged 15 30 and 60 minutes respectively after clotting The prothrombin of the residual serum is determined at 15 minute intervals The serum prothrombin determination differs from that of plasma only in that fibrinogen and labile factor must be added This is accomplished by using fresh oxalated rabbit plasma treated with tricalcium phosphate to remove prothrombin In practice 0 1 cc. of the serum to be tested is added to a mixture of 0 1 cc deprothrombinized rabbit plasma 0 1 cc of 0 02 M calcium chloride and 0 1 cc rabbit brain extract (thromboplastin) The clotting time serves as the measure of the prothrombin concentration in the serum

When prothrombin consumption is low it may be due to a deficiency of thromboplastinogen as in hemophilia or to a lack of platelet factor as in thrombocytopenia To eliminate this confusion and make prothrombin consumption the most satisfactory procedure for diagnosis of hemophilia, a new modification termed the thromboplastinogen activity test was devised

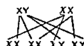
METHOD 2—The test depends on the action of heated rabbit brain extract as a platelet extract but no longer as thromboplastin To a clean 13 × 100 mm test tube containing four glass beads is transferred 0 05 cc rabbit brain extract which has been incubated at 60 C for 20 minutes Two cc of blood is added and the tube mixed

(7) Am J M S 2 3 401 413 Ap 1 195

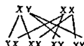
philia is a disease of males though its occurrence in females as a sex linked recessive character has always been theo retically possible If $\underline{X}$ represents the chromosome carrying this character there are two likely and three possible combinations in the inheritance of the disease (Fig 73) If the dominance of X over $\underline{Y}$ is complete only the hemo philic male $\underline{X}Y$ and the homozygous female $\underline{X}\underline{X}$ should have symptoms of the disease the heterozygous female $\underline{X}X$ being symptom free To diagnose homozygous hemophilia in the



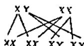
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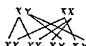
(2)



(3)



(4)



(5)

F g 73—I h ta f h m ph l (C t y f M k y C Q rt J M d 79 299 312 J ly 1951)

female the disease must be clinically and pathologically in distinguishable from that in the male both parents must have been able to transmit the affected gene and all children must show the appropriate findings on the basis of sex The ap parent absence of homozygous females probably results from the rarity of the mating required to produce such a person Union of a hemophilic man and a heterozygous hemophilic woman usually involves the marriage of cousins

In 1886 Treves described a hemophilic family in which some females appeared to be affected Merskey reinvestigated this family and traced inheritance of the disease to the sev enth generation The clinical and laboratory data are typical of hemophilia The affected women of the fifth generation re

Hemophilia Associated with Normal Coagulation Time The disease is an inherited tendency in males to bleed transmitted by apparently unaffected females No other hemorrhagic diathesis with this type of inheritance has been described Clarence Merskey[8] (Radcliffe Infirm Oxford) tested the ability of blood from a hemophilic suspect to correct coagulation time and prothrombin consumption defect in blood from a known hemophiliac in a large series of hemophilic patients Degree of abnormality on laboratory tests was shown to vary from that in classic hemophilia with prolonged coagulation time grossly defective prothrombin consumption and inability to correct hemophilic blood to a condition with normal coagulation time much less prothrombin consumption defect and partial ability to correct hemophilic blood

Of 54 patients in 8 families the coagulation time was prolonged greatly in 33 slightly in 12 and not at all in 9 The second and third groups are considered in this study In these patients clinical findings varied from mild to severe but remained relatively constant for each family When they were mild and crippling hemarthroses were absent patients led normal lives Symptoms of hemophilia were classic but hemorrhagic episodes were often widely separated Most however had had at least one severe episode requiring transfusion Dental extractions were especially troublesome

Epistaxis and easy bruising were almost invariable the latter is uncommon in normal males Hemarthrosis was uncommon in contrast to hemophilia with prolonged coagulation time If it did occur it was rarely spontaneous but usually followed severe injury In the six families with familial history the defect closely followed the classic inheritance and seemed to breed true

The importance of recognizing hemophilia with normal coagulation time cannot be overstressed Many patients had been told that surgery could be done safely and only after alarming hemorrhage was the error recognized

[Performance of the coagulation time test in silicone coated apparatus or use of the methods described in the preceding article should help to establish the diagnosis —Ed]

Occurrence of Hemophilia in Human Female is discussed by Clarence Merskey[9] (Radcliffe Infirm Oxford) Hemo

(8) B t. M J 1 906 912 Ap 1 28 1951
(9) Q rt J Med 79 299 312 J ly 1951

(Univ of Manchester England) report on a patient who had a normal pregnancy despite a history of easy bleeding but one month after spontaneous delivery had uncontrollable uterine bleeding necessitating total hysterectomy During convalescence bleeding into and infection of the incision was finally controlled by blood transfusions and antibiotics On discharge 2½ months later hemoglobin and red cell count were normal The patient was the daughter of a hemophilic father and a mother who had a hemophilic brother Her sister gave birth to a hemophilic son The patient bruised easily from childhood had occasional epistaxes and swelling of some joints Four years before she had had severe bleeding from vaginal lacerations clotting time was greatly prolonged even after blood transfusion

Three conditions resembling hemophilia that may prolong blood coagulation time in females as well as males are (1) fibrinogenopenia characterized by absence of plasma fibrinogen (2) circulating anticoagulants and (3) parahemophilia due to absence of prothrombin accelerator or labile factor

Laboratory investigations of the patient s blood were made to check it with what is known about hemophilic blood and to test the possible presence of other conditions that prolong blood coagulation Platelets were always within normal limits Whole blood clotting time by the Lee White method was consistently prolonged month after month though it was somewhat lower during the illness requiring frequent transfusions Plasma clotting time also was much above normal usually more than 15 minutes as is the case with most hemophilic subjects Plasma prothrombin time using Quick s one stage method showed 12½ to 13¾ seconds equivalent to prothrombin activity of 90 100% Plasma labile factor disappears when normal oxalated plasma is stored causing prothrombin time to increase This was normal in the patient s plasma ruling out parahemophilia Serum prothrombin time (prothrombin consumption test) a measure of prothrombin remaining in the serum after clotting was 42 105 seconds in 15 normal persons after 4 hours after 24 hours it was 85 120 seconds During the period of multiple blood transfusions the test was 19 20 seconds after 4 hours for the patient s blood after 24 hours it was 37 38 seconds After recovery in 4 hours it was 11 14 seconds and after 24 hours it was 12 15 seconds

sulted from a marriage of first cousins in the fourth The disease started early in life the patients all bled excessively from small or large wounds and hemorrhage occasionally continued for weeks The easy bruising the frequent epistaxis and hematuria and especially the attacks of hemarthrosis resulting in permanent joint deformity are all met with in hemophilia Degree of hematologic abnormality in them appears the same as that in affected males Since they were children of a hemophilic man and his first cousin this unusual occurrence can be explained by assuming that the mother was a carrier and that they were homozygous for the disease

The only anomalous laboratory observations were a positive reaction to the tourniquet test in one woman and a faintly positive reaction in another woman and one man The hemophilia was the type in which coagulation time is only a little prolonged The plasma of these patients was unable to correct the coagulation defects of known hemophilic blood to a degree at all approaching the ability of normal plasma In the absence of a circulating anticoagulant these findings are virtually diagnostic of hemophilia It is impossible to explain fully the apparently direct transmission of the disease from father to son in the first four generations Either this type of inheritance can occur in hemophilia or the record is incorrect The inheritance in later generations is of the classic type Subsequent generations are compatible with a diagnosis of homozygous hemophilia in the affected women who appear to be the first human female subjects in whom such a diagnosis has been substantiated

↓ Only with the development of modern knowledge of blood coagulation and its defects could laboratory proof of the genetic possibility be advanced as in the following article —Ed

Hemophilia in Female Hemophilia has always been considered to be limited to the male but there is one possible combination that can give rise to a female hemophiliac a male hemophiliac married to a female hemophilic carrier Since investigations of hemophilic families failed to reveal a definite hemophilic female general opinion was that the combination was lethal and that a female hemophiliac if conceived died in utero

M C G Israëls H Lempert and Elizabeth Gilbertson[1]

(1) La c t 1 1375 1380 J e 1951

(Univ of Manchester England) report on a patient who had a normal pregnancy despite a history of easy bleeding but one month after spontaneous delivery had uncontrollable uterine bleeding necessitating total hysterectomy During con valescence bleeding into and infection of the incision was finally controlled by blood transfusions and antibiotics On discharge 2½ month later hemoglobin and red cell count were normal The patient was the daughter of a hemophilic father and a mother who had a hemophilic brother Her sister gave birth to a hemophilic son The patient bruised easily from childhood had occasional epistaxes and swelling of some joints Four years before she had had severe bleeding from vaginal lacerations clotting time was greatly prolonged even after blood transfusion

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results identical with those in male hemophiliacs Addition of hemophilic normal and platelet deficient plasma to patient's plasma all gave results compatible with hemophilia in the male

The family history which appears to fulfil the requirements for producing a female hemophiliac together with the completely compatible clinical and laboratory evidence make this an undeniable case of female hemophilia

Clot Accelerating Effect of Dilution on Blood and Plasma Relation to Mechanism of Coagulation of Normal and Hemophilic Blood Stable plasma seems to owe its fluidity ex vivo to inhibiting agents which lose much activity on dilution or contact with surfaces like glass U ing recently developed technics of blood collection and processing I M Tocantins R T Carroll and R H Holburn[2] (Jefferson Med College) have demonstrated degree of fluidity of blood and disruption of equilibrium by even slight dilution

METHOD —Blood was collected in silicone coated syringes stored and tested in silicone-coated tubes Cold (4 7 C) centrifugations were done Usual anticoagulant was 19% trisodium citrat Blood was aspirated without bubbling through 18 gauge needles after quick puncture of a turgid vein at 0 5 ml or more per second centrifuged at 3 000 rpm for one hour and the upper three fourths of the plasma removed with silicone coated droppers measured with siliconized graduated pipets and tested within an hour

Experimental observations indicated that dilution with 0 85% NaCl solution accelerates coagulation of both normal and hemophilic blood and plasma the hemophilic more notably Shortest clotting times of normal blood are obtained with 50-70% concentration of normal plasma with 30 50% Normal and hemophilic plasmas have shorter clotting times in concentrations of less than 70% than when undiluted Carefully collected and centrifuged normal plasma with minimal dilution by citrate and calcium solutions will not clot in concentrations of 80% or above Citrated hemophilic plasma diluted five times with 0 85% NaCl clots at nearly the same rate as undiluted normal plasma Usually to bring coagulation of these plasmas to about the same rate hemophilic plasma must be diluted 10 20 times Therefore if delayed coagulability of hemophilic blood were due to insufficiency of accelerator

(2) Blood 6 7 0 739 A gust 1951

dilution of either blood or plasma should accentuate the defect and delay coagulation rate

On the basis of this and other types of experiments a tentative hypothesis is proposed Normal circulating blood and plasma in contact with inert surfaces maintain their fluidity and coagulability by equilibrium between clot inhibiting and clot promoting forces Under normal conditions clot inhibiting forces are dominant though procoagulant substances are present in excess of that needed for rapid clotting Inhibitors may be bound to procoagulants holding them in inactive form (antiprothrombin antiaccelerator globulin action) the clot accelerating effect of dilution on stable plasmas favors this Inhibitors may inactivate the effect of released coagulants (antithromboplastin antithrombin action) Reduced activity of cephalin thromboplastin and thrombin after incubation with stable plasma or serum makes this explanation plausible Clotting may then be initiated by release of procoagulant in its active forms Contact with certain surfaces dilution of blood exposure to by products of blood and tissue cell disintegration are some disturbing forces which may help to determine these changes In hemophilia dissociation of an accelerator/inhibitor complex (Ac globulin/anticephalin?) is slowed by an excess of inhibitor Greater dilutions more thromboplastin (or platelets) or longer contact with certain surfaces are therefore required to free accelerator from inhibitor after this hemophilic accelerator is as active as that obtained from normal plasma

[This challenging article with its numerous carefully described experimental procedures deserves study in the original To many investigators the conclusions are unorthodox —Ed]

Congenital SPCA Deficiency Hitherto Unrecognized Coagulation Defect with Hemorrhage Rectified by Serum and Serum Fractions Subnormal concentrations of factor V (parahemophilia) plasma Ac globulin and labile factor result in retarded prothrombin conversion conversion and in hemorrhagic phenomena despite normal prothrombin levels Clinical and laboratory investigations of a case are reported by B Alexander R Goldstein G Landwehr and C D Cook[3] (Boston) providing evidence of an additional constituent involved in prothrombin conversion which may cause a hemor

(3) J Cl I t 30 596 608 J 1951

rhagic diathesis hitherto unrecognized simulating hypopro thrombinemia

Girl 4 was hospitalized with bloody stools for three days and hematemesis for six hours The mother and maternal uncle bruised easily and the maternal grandfather died of intestinal bleeding following trauma The patient an only child had prolonged umbilical cord bleeding at birth and passed gross blood per rectum until age 5 weeks At that time blood and platelet counts and bleeding and clotting times were normal Prothrombin time was not determined Results of x ray study with barium enema were negative but laparotomy was performed because of melena No cause for the bleeding could be found Convalescence was uneventful except for mild melena which continued for several months The child bruised easily and had spontaneous epistaxis occasionally

Physical examination revealed pallor Temperature was 99 F pulse 130 respirations 30 blood pressure 100/50 There were a few small ecchymoses on the left leg abdomen and forehead but no petechiae Clotted blood but no bleed points were seen in the nose Heart was slightly enlarged to the left Red cell count was 1 040 000 hemoglobin content 6 0 Gm white cell count 14 800 with normal differential platelets 412 000 recticulocytes 7 5% sedimentation rate 4 mm /hour hematocrit reading 17% Six urine specimens were normal stools were repeatedly guaiac positive for three days and negative thereafter Bleeding time (Duke) was 12 5 minutes clotting time 6 minutes clot retraction normal Prothrombin time was 72 seconds (control 17)

Treatment with fresh whole blood and vitamin K brought about symptomatic improvement but the prothrombin time remained up and four months after discharge was still 62 seconds

The prothrombin time consistent with only 3% normal prothrombic activity was not due to prothrombin deficiency since by the two stage method the prothrombin level was consistently within normal limits Defects of Ac globulin (labile factor) or of fibrinogen and presence of anticoagulants such as antithrombin antithromboplastin or any other anticoagulant were excluded

SPCA (serum prothrombin conversion accelerator) a substance distinct from Ac globulin is considered to be the autocatalytic accelerator of thrombin formation potentiating the action of thromboplastin The patient s SPCA activity was abnormally low despite normal prothrombin consumption in the two stage method and accelerating the clotting of her freshly shed blood with thromboplastin supplements failed to increase formation of SPCA in contrast with normal blood Plasma prothrombic activity by the one stage method de

creases during storage because of deterioration of labile fac tor In a modified procedure in which aged plasma is diluted with fresh $BaSO_4$ plasma stored plasma shows increased pro thrombic activity because prothrombin conversion accelerator identical with SPCA is evolved This phenomenon was not demonstrable in the pathologic plasma

Normal serum mixed with pathologic plasma decreased the prothrombin time but the patient's serum was relatively inert on her own as well as on normal plasma The same re sults were obtained when purified SPCA fractions were sub stituted for normal serum Also removal of SPCA from nor mal serum by $BaSO_4$ adsorption rendered it inert Hypopro thrombinemic dicumarol® plasma also could induce thrombin evolution in the patient s plasma but $BaSO_4$ adsorption of the dicumarol® plasma decreased its effect

The in vitro effect of normal serum suggested its use as a therapeutic agent and she was given 150 ml 24 hour old normal serum slowly Prothrombin time decreased notably for several hours but gradually increased to its previous level within 24 hours

Case of Congenital Familial Afibrinogenemia is reported by A Bucek[4] (Novy Jicin Czechoslovakia) Hemorrhagic dis ease due to lack of fibrinogen is rare Glanzmann makes a dis tinction between constitutional inborn afibrinogenemia and fibrinopenia as a constitutional defect transmitted to the off spring or as a result of liver or bone marrow disease

Girl 12 was hospitalized because of persi tent bleeding from the nose and gingiva Two brothers had bled from the umbilicus after birth of which one died At age 3 the other brother died of intra cranial hemorrhage following an accident At age 2 the patient bled profusely for three days after being cut by a cythe At age 6 she bled profusely after extraction of a tooth Blood studies showed 4 430 000 red cells 523 000 platelets and hemoglobin value of 55% Bleeding time was 30 minutes and clotting time 75 minutes Physi cal examination showed asthenia bleeding from the nose and gingiva and hematomas on the right leg The liver and spleen were not palpable temperature was normal Blood studies were again made Results were 3 170 000 red cells 12 000 white cells (normal dis tribution) and hemoglobin value of 60% Bleeding time was 30 minutes there was no clotting after 18 hours Blood transfusions were given a total of 400 cc After injections of calcium vitamins K and C bleeding stopped On discharge bleeding time was three minutes and clotting time six minutes

(4) A p d t 177 111 115 A gu t 1951

At age 12 she was rehospitalized In addition to the symptoms present at age 6 she had impetigo Blood studies showed 2 470 000 red cells 10 200 white cells and hemoglobin value of 50% Bleeding time was 5 minutes and clotting time over 20 minutes Resistance of red cells was normal Addition of normal plasma to that of the patient caused clotting whereas addition of serum failed to do so which proved lack of fibrinogen Plasma protein studies showed 2 68% albumin and 1 697% globulin fibrinogen did not precipitate The same treatment was given as previously with the same result.

When the patient was rehospitalized 1 year later she was febrile and subicteric Two days later she had mumps and hematemesis and hematomas appeared on both legs There were 69 520 platelets clotting time was over three days Bleeding stopped after transfusion of 150 cc mother s blood Ten days later she had melena (70 cc pure blood) Platelets numbered 200 000 The Takata Ara test gave a negative reaction Icterus intensified after two blood transfusions (400 cc) The indirect van den Bergh test gave a positive reaction the direct a negative reaction The spleen was palpable the liver extended over the costal arch about 2 fingerbreadths She was discharged on request At this time blood studies showed 1 320 000 red cells 14,200 white cells with left shift and hemoglobin value of 23% The icterus was considered homologous serum jaundice

[This rare condition is al o remarkable because the patients may for considerable periods and despite completely incoagulable blood experience no significant hemorrhages According to Dr H A Lawson menstruation may even be normal —Ed]

Cause of Blood Coagulation Defect Following Abruptio Placentae Abruptio placentae is sometimes followed by a hemorrhagic syndrome which results from sudden depletion of plasma fibrinogen Ernest W Page Lee D Fulton and Mary Beth Glendening[5] (Univ of California) determined plasma fibrinogen concentrations in six cases in three of which values were normal In the fourth case toxemia with severe separation was followed by a hemorrhagic state and irreversible shock Autopsy revealed total infarction of the liver with numerous fibrin deposits in and around the blood vessels The plasma contained no fibrinogen In the other two cases of severe placental separation fibrinogen concentrations were reduced almost to critical levels even though no hemorrhages resulted (probably because of multiple transfusions) In none did the undiluted plasma clot show evidence of lysis when placed in an incubator at 37 C for 24 hours

In vivo defibrination was produced in 18 dogs by slow intravenous infusion of human placental thromboplastin Be

(5) Am J Obst & Gynec 61 1116 1122 May 1951

fore during and after infusion observations were made on clotting time sedimentation rate plasma fibrinogen concen tration and prothrombin concentration with and without added accelerator globulin Plasma clots were incubated to note possible lysis In addition attempts were made to isolate and assay quantitatively amounts of circulating thrombo plastin and liver and kidney biopsies were performed There was some variability in quantitative results from animal to animal but qualitatively results were similar Changes in cluded fibrinogen depletion a reduction in prothrombin and accelerator globulin concentrations inability of the blood to clot focal lesions in liver and kidneys and oliguria All these changes are sometimes encountered in severe abruptio pla centae Administered thromboplastin disappeared almost im mediately from the blood and was probably incorporated with fibrin and fixed by the tissues No fibrinolytic activity was demonstrated in undiluted plasma samples from 10 of the dogs

The authors are skeptical about the importance attributed to fibrinolysis by others and believe that defibrination is due to escape of placental or decidual thromboplastin into the ma ternal circulation This converts prothrombin to thrombin which in turn converts fibrinogen to fibrin the latter is de posited spottily over an extensive vascular surface sometimes producing serious visceral lesions

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON M.D

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Transposition of Aorta and Pulmonary Artery is discussed by Maurice Campbell and S Suzman[1] (Guy s Hosp London) Typical clinical features are deep cyanosis increased pulmonary blood flow (pleonemic lungs) with pulsating pulmonary arteries a loud pulmonary second sound and right ventricular hypertrophy Nine of 25 patients were aged 6 18 16 being 5 or less Correct diagnosis is important since the condition may be mistaken for tetralogy of Fallot Usually the heart is large Murmurs are not typical although there is generally a systolic one loudest at the apex Many children have none A fourth of the patients had a diastolic murmur Prognosis depends on size of the shunts between the left and right sides (transposition may be partial or complete) life expectancy is not as short as was once believed When shunts are large enough to permit good mixing of the two circulations the patient may reach childhood in fairly good health Absence of cardiomegaly in early life is a good prognostic sign In this series ECG s showed no features different from those seen in tetralogy of Fallot In six patients cardiac catheterization showed typical and diagnostic finding of higher O content in the pulmonary artery than in the aorta and its branches Right ventricular and pulmonary artery pressures were high and there was evidence of a ventricular septal defect with left to right shunt Angiocardiograms in seven patients showed transposition of the aorta and delayed pulmonary artery filling despite the increased flow

In two additional cases complete transposition of the aorta and partial or complete transposition of the pulmonary artery were complicated by infundibular pulmonary stenosis Therefore differentiation from tetralogy of Fallot was even more

difficult since there were no prominent pulmonary artery pulsations

The authors stress that in any child with severe cyanosis pleonemic lungs and pulsating pulmonary arteries transposition of the aorta and pulmonary artery must be considered present until proved otherwise

[The clinical and ECG findings may be quite similar in patients with transposition and with the Eisenmenger complex However with the latter cyanosis is likely to be slight or absent during infancy and childhood and to increase as pulmonary resistance rises and the degree of right to-left shunt increases With transposition there is usually a history of well marked cyanosis throughout life —Ed]

Right Heart Catheterization in Patent Ductus Arteriosus and Aortic Pulmonary Septal Defect Forrest H Adams Antoni Diehl Joseph Jorgens and L George Veasy[2] (Univ of Minnesota) report results in 24 patients aged 1½ 18 with patent ductus arteriosus or aortic pulmonary septal defect proved at surgery Eight had typical clinical signs of patent ductus before cardiac catheterization Atypical signs were evident in 16 6 of whom were thought to have aortic pulmonary septal defect after cardiac catheterization and after results had been correlated with clinical data

Of the patients with typical cases two had right ventricular and pulmonary artery pressures above normal Left to-right shunt through the ductus varied from 0 5 to 15 2 L/minute (representing 7 66% of the left ventricular output) Of the patients with atypical findings (excluding those with aortic pulmonary septal defect) two had only systolic murmurs over the left precordium and were thought to have an intra atrial septal defect Six had abnormal ECG s three with right axis deviation Six had x ray findings not consistent with patent ductus Cardiac catheterization clearly established the diagnosis of left to right shunt through a patent ductus (in three instances the catheter was passed through the ductus) In this group the shunt varied from 0 8 to 11 1 L/minute (24-67% of left ventricular outflow) Seven patients had moderate cardiac disability

Only one patient with aortic pulmonary septal defect had a machinery murmur The others had a systolic murmur with or without a diastolic murmur best heard in the third and fourth left interspace Five had abnormal ECG s with

(2) J Pediat. 40 49 59 January 1952

right axis deviation in two and large biphasic QRS complexes in four Half the group on roentgen examination were thought to have Lutembacher s syndrome On cardiac catheterization all but one proved to have right ventricular and pulmonary artery hypertension The shunt varied from 4 4 to 21 9 L./minute (46-85% of left ventricular output) Four patients had mild to moderate cardiac disability The catheter was passed into the aorta in one instance One patient with a large defect died during operation Another was shown to have an enormous patent ductus rather than the suspected defect in addition to an intraventricular septal defect

In all patients there was only poor correlation between the amount of shunt flow and cardiac disability Several patients with large shunts had no disability but all with mild to moderate disability had sizable shunts There was better correlation between cardiac symptoms and pulmonary hypertension All patients with no disability had normal pulmonary artery pressures whereas most of those with disability had pulmonary hypertension Very large shunts were present in several instances without pulmonary hypertension but all but one patient with pulmonary hypertension had large shunts

The five cases of aortic pulmonary septal defect diagnosed within two years indicate that the condition is not as rare as previously believed

Patent Ductus Arteriosus Observations on Diagnosis and Therapy in 525 Surgically Treated Cases are presented by Robert E Gross[3] (Harvard Med School) Patent ductus arteriosus is commoner in females (70%) In general it is tolerated well in childhood although in some there may be retarded physical development Patients in midlife often have moderate cardiac embarrassment less commonly they have the classic signs of failure Simple examination leads to diagnosis in over 95% of cases Cyanosis is never found unless there are frank cardiac failure and reversal of blood flow through the ductus The nails are not clubbed The heart is normal or slightly increased in size great enlargements are rare Systolic blood pressures are normal The diastolic level is likely to be depressed depending on size of the aortic leak

A characteristic murmur is heard in the second or third intercostal space to the left of the sternum It is continuous

(3) Am. J Med 1 47 48 Ap 1 1952

and is accentuated during systole and dies off during diastole The pulmonic sounds may be replaced by the murmur or the second sound may be quite accentuated Although all of the murmur may be transmitted it is commoner to have only the louder systolic portion carried to the cardiac apex neck or back Generally any loud systolic murmur (unaccompanied by a diastolic element) in acyanotic congenital heart disease comes from a septal defect or pure pulmonic stenosis Few patients have only a systolic murmur The classic sounds of an open ductus may not be found if a patient (usually an adult) is being examined during failure About half the patients have a thrill It may be continuous or limited to systole it is most intense over the pulmonic region and seldom felt far from there Peak incidence of endocarditis or pulmonary endarteritis comes in the third and fourth decades diminishing thereafter Often it is impossible to hear a murmur in infancy the murmur appears later when aortic pressure has risen Some babies with ductus have a continuous and easily recognizable machinery murmur from birth

The ECG is of no aid in diagnosis but is useful in determining extent of myocardial strain or presence of other anomalies Catheterization confirms the diagnosis in obscure cases but is not often necessary If there is no characteristic murmur too much reliance should not be placed on laboratory or roentgen observations (other than catheterization) which might suggest ductus because thoracic exploration in such circumstances generally discloses some other cardiovascular defect

Although patent ductus usually seems innocuous in childhood the outlook is serious Subjects alive at age 17 have a life expectancy averaging only about half that of the general population Surgery is recommended for (1) children with stunted development (2) all patients with failure and (3) those mostly in the third and fourth decades with no ordinary signs of cardiac failure but with great fatigue In superimposed endocarditis if the blood cannot be sterilized by chemotherapy alone operation should be performed during the active stage otherwise surgery should be performed later Low mortality and absence of postoperative complications make intervention advisable even in young asymptomatic patient but it should be avoided in asymptomatic patients

beyond midlife In patients who have any cyanosis and also auscultatory sounds of patent ductus the ductus should never be closed surgically either the patient is in terminal failure due to a large ductus or a ductus is acting as a compensatory mechanism for a complicated cardiovascular defect If there are pressing indications operation should be undertaken without regard for the patient s age or size For the elective cases optimal ages are 3 4 up to 15 20 best chances for a smooth and relatively easy surgical procedure are generally present between 6 and 12

Of 482 patients who had complete division 10 died In those with only minor symptoms before operation mortality rate was less than 0 5% After the operation diastolic blood pressure rose immediately the extent varying with the extent of depression before operation The continuous machinery murmur always disappeared a few had a soft systolic murmur believed to be functional About 6% had a residual murmur undoubtedly due to a second cardiac defect Patients with essentially normal physical development before operation showed no important changes after surgery Underweight subjects most of whom were children often gained weight Obliteration of the shunt can greatly diminish output of the left side of the heart Presumably the cardiac reserve is accordingly improved

Double Aortic Arch Clifford F Storey and J W Crittenden[4] (U S Naval Hosp St Albans N Y) report a case

In a boy born Nov 18 1949 respirations were established immediately but because of pronounced stridorous breathing and cyanosis laryngoscopy was done in the delivery room No upper respiratory abnormality could be found In other respects he was normal He had constant and severe stridor with pronounced retraction of the lower sternum excessive secretion of mucus and intermittent cyanosis Chest roentgenogram were repeatedly negative He took the bottle well but each feeding was prolonged because of shortness of breath Results of fluoroscopy with thin barium were inconclusive Bronchoscopy showed the posterior membranous wall of the trachea markedly displaced forward immediately above the carina at the level of the aortic arch and definite pulsation at the site of the posterior compression In the same area each lateral wall of the trachea was compressed from without and displaced medially so that the tracheal lumen on inspiration presented as a triangular opening On expiration it narrowed to a tiny crevice or minute slit With thick barium the deformity was clearly visualized In the

(4) D Ch st 0 611 6 9 D mbe 1951

lateral projection striking indentation of the posterior esophageal wall was seen at the level of the aortic arch whereas in the anteroposterior view bilateral compression of the esophagus was noted The esophagus above the point of obstruction was considerably dilated The barium passed the point of obstruction only slowly in a thin intermittent trickle What appeared to be two aortic knobs were seen one on either side with the left slightly higher than the right There was no appreciable difference in their size

On left thoracotomy on Feb 16 1950 the chest was entered through the second anterior interspace An apparently normal aortic arch gave rise to the left common carotid and left subclavian arteries at the usual sites The ligamentum arteriosum which ran in the usual manner from the aortic arch was divided The descending aorta was not seen in the expected position Dissection along the aortic arch distal to the left subclavian artery showed the arch coursing transversely across the mediastinum posterior to the trachea and esophagus and disappearing in the right chest Further dissection disclosed a double aortic arch The somewhat smaller left arch was freed throughout its circumference and temporarily occluded just distal to its origin and proximal to the point where it gave rise to the left carotid carotid and subclavian pulsations were undiminished which established that the left arch joined the right in the right chest after passing behind the esophagus and that it could receive blood from either direction The left arch was therefore divided

Immediately after operation the infant breathed easily and quietly without stridor or sternal retraction for the first time in his life However progressive laryngeal edema rapidly developed and required tracheotomy He did poorly and died seven weeks later

Pulmonary Stenosis with Normal Aortic Root D Gordon Abrahams and Paul Wood[5] (Brompton Hosp) report 71 cases (12% of all cases of congenital heart disease) There were 37 patients with simple pulmonary valve stenosis and 8 with simple infundibular stenosis Accurate bedside diagnosis was nearly always possible Severe cases were characterized by effort intolerance peripheral cyanosis moon facies small peripheral pulse giant *a* waves in the jugular venous pulse presystolic hepatic pulsation tapping cardiac impulse parasternal right ventricular heave impalpable pulmonary artery high pulmonary systolic thrill and murmur and single second heart sound The ECG showed the P pulmonale and strong right ventricular dominance X rays showed pulmonary ischemia poststenotic dilatation of the pulmonary artery and enlargement of the right ventricle and atrium Catheterization

(5) Brit Heart J 13 519 548 Octobe 1951

revealed mean right ventricular pressure over 40 mm Hg and systolic pressure often well above systemic pressure Pulmonary artery pressure was low (2 10 mm Hg) Atrial systole generated a pressure of around 10 mm Hg The cardiac output was low and relatively fixed

Infundibular stenosis may be distinguished from valve stenosis by the low position of the thrill occasionally by absence of a parasternal lift by absence of dilatation of the pulmonary artery and by cardiac catheterization Patients with mild valve or infundibular stenosis are symptom free and show little abnormality beyond the systolic thrill and murmur and poststenotic dilatation of the pulmonary artery (in the valvular type)

In 15 patients pulmonary stenosis with normal aortic root was complicated by an arteriovenous intracardiac shunt 8 through a ventricular and 7 through an atrial septal defect In about half the main clinical features were those of pulmonary stenosis in the rest the signs were determined chiefly by the septal defect Pulmonary stenosis with normal aortic root complicated by reversed interventricular shunt was encountered only once This condition closely resembled Fallot s tetralogy and is only distinguished at autopsy There were eight cases of pulmonary stenosis with reversed interatrial shunt through an atrial septal defect or patent foramen ovale Stenosis was always severe Such cases may be distinguished from Fallot s tetralogy by the history by giant *a* waves and presystolic hepatic pulsation by the degree of left parasternal heave and by poststenotic dilatation of the pulmonary artery Three patients with simple pulmonary valve stenosis had a functionless probe patent foramen ovale through which a catheter was passed

Two patients had acquired pulmonary stenosis one with syphilis and the other due to mediastinal cyst or tumor Bacterial endocarditis improved two severe cases of pulmonary valve stenosis Clinical pulmonary tuberculosis occurred in only 1 of the 69 patients with congenital stenosis autopsy revealed an unsuspected Ghon focus in another Pulmonary valvulotomy was done in 10 severely ill patients 3 died 4 were greatly improved and 2 recently operated on were doing well

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(5) B t H a t J 13 519 548 Octobe 1951

RHEUMATIC HEART DISEASE

Rheumatic Fever and Rheumatic Heart Disease Twenty Year Report on 1,000 Patients Followed Since Childhood is presented by Edward F Bland and T Duckett Jones[7] (Boston) The patients first seen in 1921 31 had rheumatic fever chorea or rheumatic heart disease Average age at onset was 8 patients over 20 were excluded

On recovery from the initial illness 653 patients had signs of rheumatic heart disease 20 years later 108 (16%) had none In no case did an aortic diastolic murmur of grade 2 or greater intensity or the signs of established mitral stenosis disappear Of the 347 patients who recovered from the initial illness without detectable heart disease 154 (44%) had signs of valvular disease after 20 years Chorea had been prominent in this latter group in only a third was there clear evidence of recurring rheumatic activity

In the first 10 years 202 patients died after the second 10 years 301 had died Rheumatic fever and congestive heart failure accounted for 80% of the deaths and bacterial endocarditis for 10% A greatly enlarged heart or congestive failure early in the disease exacted the highest toll with 80% mortality in 20 years Pericarditis subcutaneous nodules and acute arthritis occupied intermediate positions with 63 37 and 27% mortality rates over the two decades In contrast chorea was associated characteristically with a benign form of the disease (12% mortality) There was of course much overlapping of symptomatology Recurrence of rheumatic fever or chorea was noted in 20% in the first five years 10% during the next five years 5% during the third five year interval and a low percentage in the final five years

Of the 87 who originally had only a grade 2 or greater systolic murmur at the apex in about a third the murmur disappeared in a third it was unchanged and in a third there was slow progression of physical signs with acquisition of a diastolic murmur at the apex The course of this group was most benign in terms of disability and death A pure form of

(7) C cul tion 4 836-843 D mbe 1951

Interauricular Septal Defect Correlation of Clinical, Radiologic and Electrocardiographic Findings in 15 Cases with Special Reference Given to Electrocardiogram was attempted by Ned W Smull and Lawrence E Lamb[6] (Univ of Kansas) Diagnoses were made clinically and in only one instance was there an autopsy to support the clinical diagnosis Cardiac murmurs systolic in character were present in all Cardiac enlargement was noted in nine patients four showed clear evidence of heart failure with enlarged and palpable liver Seven had a definite precordial bulge eight were underdeveloped Five had a history of intermittent cyanosis chiefly when the child cried Troublesome upper respiratory infections were frequent and five had had pneumonia

X ray showed prominent pulmonary arteries in 10 patients a hilar dance observed by fluoroscopy in eight was useful in differentiating hilar shadows due to increased vascularity from those of nonvascular origin Evidence of right heart enlargement was fairly clear in 12 in 2 of these right heart enlargement was seen only on the right anterior oblique views In three patients x ray showed no cardiac enlargement yet ECG showed right ventricular hypertrophy The ECG features encountered included enlarged P waves associated with auricular enlargement (2 cases) right ventricular hypertrophy as manifested by delay in intrinsicoid deflection (all 15 cases) and right axis deviation (10 cases) associated with right ventricular enlargement and conduction defects in the form of right bundle branch block (one case) auriculoventricular block (10 cases) auricular tachycardia and auricular fibrillation Thus no specific patterns were seen that were absolutely diagnostic However accurate diagnoses can be made with proper correlation of the clinical roentgen and ECG findings Clinically the lesion does not appear as innocuous in children as some suggest Heart failure does occur Upper respiratory infections which are common should be guarded against because of their complicating sequelae

Differential diagnosis includes other congenital heart defects of the acyanotic type patent ductus arteriosus ventricular enlargement isolated pulmonic stenosis and interventricular septal defect

(6) Am Heart J 43 481 493 Ap 1 1952

4 three and 3 five or more relapses Of 44 patients with articu lar symptoms 34 had had them ever since the rheumatic fever some since a subsequent relapse and 10 after a symptom free interval Objective joint signs were found in only 25 patients

Among the 39 patients reported on by a physician or hos pital only 1 could with certainty be thought to have chronic rheumatic heart disease Another had a presystolic apical murmur Complaints of cardiac and joint symptoms were of much the same frequency as in the patients personally ex amined

Effects of Cortisone and ACTH on Acute Phase of Rheu matic Fever Arlie R Barnes[9] (Mayo Clinic) treated 14 pa tients 10 with cortisone and 4 with ACTH Results depend on severity of the disease and how early treatment is started If the hormones are given early polyarthritis fever and tachy cardia usually disappear in a few days The P R interval is usually normal in 2 weeks and sedimentation rate in 12 21 days Hemoglobin and serum globulin values become normal in a few weeks and antistreptolysin O titers fall When how ever therapy is discontinued all symptoms and abnormal values usually reappear within two weeks Therefore the hor mones are thought to act directly on the tissues to suppress the proliferative reactions in the heart and thus prevent later development of chronic disease They probably do not cure acute rheumatic fever but may shorten its course

The well known specific effects of the hormones are some times observed Although there may be retention of salt and water with formation of edema this was not observed in Barnes series If it does occur mercurial diuretics and low salt diet (less than 0 5 Gm sodium daily) easily control it Hypochloremia and hypopotassemia may develop but are counteracted by 2 4 Gm potassium chloride daily

In acute rheumatic fever 200 mg cortisone should be given intramuscularly daily for 3 14 days When acute mani festations have subsided 100 mg is given for two to four weeks then 75 mg daily or 100 mg every other day until the disease is believed at an end Increased sedimentation rate with prolonged P R interval and/or joint symptoms is prob ably an indication for resumption of treatment

If ACTH is used initial doses of 45 60 mg daily are sat

(9) C 1 t 3 770 775 M y 1951

mitral stenosis (without systolic murmur) developed in 117 patients but in only 12 did evidence of serious pulmonary hypertension appear Even this pure form need not always represent a high degree of stenosis, and slight degrees accompanied by little or no cardiac enlargement were present for years without serious disability or apparent progression The suggestion that early valvulotomy might prevent the development of greater obstruction seems too drastic The aortic valve was involved (characteristic blowing diastolic murmur) initially in 194 patients and later in 179 others In 27 the aortic diastolic murmur was the only evidence of cardiac involvement the rest had coexisting signs of mitral valve disease In nine the diastolic murmur of slight aortic regurgitation disappeared in later years in 27 the aortic systolic murmur accompanying the characteristic diastolic murmur slowly increased to a degree indicating development of considerable stenosis In only two did uncomplicated aortic stenosis become established

After 20 years 699 of the original 1 000 patients were alive Most were remarkably well Three out of 4 had little or no limitation 76 had served in the armed forces and 421 children were born to the female patients with minimal complications

Follow up Study of Patients with Rheumatic Fever, with Special Reference to Chronic Cardiac and Articular Disease Else Arnsø Knud Brøchner Mortensen and Bent Hastrup[8] (Copenhagen) discuss 194 patients (73 males) hospitalized with rheumatic fever in 1926-40 Sixteen died during hospitalization Of 173 traced in 1949 23 had died in 3 of these presence of rheumatic heart disease was ascertained and 6 had had cardiac disease which may have been rheumatic

Among the 91 patients examined on follow up 46 had subjective cardiac symptoms functional dyspnea (43%) and more or less pronounced sensations over the precordium However definite symptoms of chronic rheumatic heart disease were found in only 11 and in another 3 it was suspected although diagnosis could not be established Two patients with rheumatic heart disease had no complaints the others had various cardiac complaints but were all fit for work Of 31 patients with one or several relapses 15 had had one 9 two

(8) A ta med d 141 77 88 1951

pressure fell to normal amount of hexamethonium was thus automatically adjusted if wide swings occurred part of the dose was omitted at chosen levels Patients were then discharged to home care dosage being constantly adjusted according to blood pressure readings taken by a member of the family if possible Maximal doses totaled 6 Gm hexamethonium chloride and 900 mg 1 hydrazinophthalazine daily smallest effective doses were 375 and 75 mg respectively

Benign arterial hypertension was controlled at normotensive or nearly normotensive levels in all of 25 patients Continuous administration was essential Slight postural hypotension resulting from unsuccessful sympathectomy was greatly enhanced In 15 patients malignant hypertension responded variably to parenteral and oral administration of the preparations some were later well controlled with oral doses whereas others were only partially controlled and two were affected only temporarily The malignant stage was altered favorably in all but two The method was practical for use at home by intelligent patients It represents a means of controlling hypertension but in no sense is a cure No tolerance to these agents appeared after normotension had been established in fact patients tended to use less hexamethonium after a month or two of normal blood pressure

Long term results cannot be evaluated until more time has elapsed During this short term study certain pathologic signs secondary to chronic hypertension regressed toward normal

The toxic effects of hexamethonium are attributable to its primary action i e autonomic paralysis Fortunately the doses used in most cases were so small that serious side actions were not encountered Constipation was almost always present Other reactions all minor included blurring of vision in hyperopic persons dryness of the mouth minor digestive disturbances retention diminished sweating warm dry hands and feet and disturbances of regulation of body temperature on hot or cold days These effects tended to disappear as the drug was continued Toxic effects of 1 hydrazinophthalazine are attributable to its suppression of histaminase activity In patients with hypertensive headaches most of which are probably histaminic in origin they may be induced by this drug Although headaches eventually disappear as dosage is con

isfactory In critically ill patients however as much as 100 mg may be given daily for a few days The dose is reduced as with cortisone Usual maintenance dose is 25-40 mg daily *All intramuscular doses are best given in divided portions* three or four times daily Severity of the disease not the patient s age or weight is the best guide to dosage

ACTH or cortisone was given 10 patients during the first attack and 1 during a recurrence Re examination 1 18 months after discharge showed that six had no cardiac signs or symptoms Two of these later had a recurrence

Five patients given cortisone had carditis Two weeks of treatment caused striking improvement in three who had been ill for 15 16 and 40 days whereas improvement was noted after 4 weeks in a fourth patient who had had acute rheumatic fever for 43 days In the patients the heart size was reduced and appetite and morale were greatly improved

Barnes concludes that hormonal treatment should be be*gun early and continued for the natural duration of the dis*ease the aim being suppression of the acute manifestations

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HYPERTENSION

Control of Hypertension by Hexamethonium and 1 Hydrazinophthalazine Preliminary Observations are reported by Henry A Schroeder[1] (Washington Univ) Patients were selected only to the extent that they had chronic arterial hypertension severe enough for hospitalization and enough resistance to ordinary therapy that prognosis seemed poor *The* usual procedure was to administer 125 250 mg hexamethonium chloride every eight hours dosage being increased until 500 *mg* every four hours was reached or sustained hypertension had been converted into blood pressure showing wide fluctuations which reached normal levels At this point 1 hydrazinophthalazine was added 25 50 mg every eight hours the amount being increased until *100 mg every four hours* was reached or blood pressure had become normotensive Blood pressure was determined before each dose was given and hexamethonium was omitted if systolic pressure was below 120 mm Hg (or 130 140 mm Hg in older persons) As blood

(1) A M A Arch I t M d 89 523 540 Ap 1 195

was no improvement in urea retention one died in uremia after several months of treatment The rest followed two to eight months were doing well considering the seriousness of the original condition with blood pressures remaining low Two patients had hypotensive attacks during therapy and one had elevated blood bromide values and was changed to the bitartrate preparation

In six tense hard driving patients blood pressure re mained elevated despite hospitalization bed rest and sedation there was little evidence of renal damage Hexamethonium bromide (maximum dose 3 Gm daily) caused no significant drop in blood pressure even on standing Three then given hexamethonium bromide intramuscularly 300 400 mg in 24 hours had abrupt falls in blood pressure never lasting over an hour In one patient headache was alleviated by this transi tory fall but the drug made him feel miserable The two others appeared to develop tolerance

Nineteen patients had a marked fall in blood pressure soon after hospitalization even though not confined to bed Al though co operative and relaxed all showed the effects of hypertension e g cerebral vascular accidents in seven mild myocardial failure in four severe angina pectoris in one and hypertensive retinopathy and ECG abnormalities in all Hexa methonium bromide or bitartrate for one to five months caused postural fall of blood pressure and impressive sense of well being Blood pressure readings seemed lower after dis charge than before hospitalization Generalized malaise de veloping in five patients with elevated blood bromide levels (highest 80 mg/100 cc) was relieved on change to the bitartrate Moderate constipation was easily overcome There was no mouth dryness or visual defect Two patients had serious vascular accidents during therapy

Use of Purified Veratrum Viride Alkaloids in Treatment of Essential Hypertension was tested by J Gordon Barrow and Clayton R Sikes[3] (Emory Univ) on 25 patients aged 28 60 with average blood pressure 160/100 mm Hg or more Blood pressures were taken from the left arm after the pa tient had been supine for 10 minutes The patients visited the clinic monthly during the control period of two to six months When treatment was started they were seen weekly The drug

(3) Am H t J 41 74 748 M y 1951

tinued prostration nausea and vomiting can be serious complications for several days Prior administration of hexamethonium prevented this action of 1 hydrazinophthalazine No cumulative toxic effects were observed in patients taking 1 hydrazinophthalazine alone for a year or more The toxic effects of both drugs taken in combination are caused by severe hypotension which is rapidly induced in subjects with organic vascular disease and causes ischemia of the brain myocardium or kidney

[These new blood pressure lowering drugs can induce severe hypotensive symptoms The procedure advocated by Schroeder is somewhat cumbersome and is expensive as it involves hospitalization for a period of several weeks On the other hand it has the great advantage of minimizing toxic reactions and of determining accurately the dosage requirements which fluctuate conspicuously from one patient to another and even in the same patient from time to time On the basis of personal experience admittedly limited I believe this plan of management is at present decidedly the preferred treatment for patients with severe hypertension It appears to be definitely superior to the use of veratrin compounds and will quite possibly supplant sympathectomy entirely On the other hand the use of hexamethonium chloride and 1 hydrazinophthalazine without adequate control of dosage by blood pressure measurements appears to be hazardous —Ed]

Hexamethonium Compounds in Treatment of Hypertension C W, Fullerton and I G Milne (Montreal Gen l Hosp) treated 31 hospitalized patients Blood pressure readings were taken every four hours for several days to several weeks before therapy The patients if able were purposely not confined to bed At first 250 mg hexamethonium bromide orally was given as a test dose followed the next day by 250 mg four times thereafter the dose was rapidly increased to 3 Gm daily Latterly five patients were given hexamethonium bitartrate with maximal dose 4 Gm daily Bromide intoxication was carefully watched for and blood bromide determinations were often made Patients were arbitrarily divided into three groups

Six patients had severe hypertension with albuminuria fixation of urinary specific gravity and greatly elevated blood urea and creatinine levels Four had agonizing headaches In all small doses of hexamethonium reduced blood pressure without renal shutdown and relieved headache Two moribund patients given intramuscular injections (15 mg average dose) showed remarkable response with blood pressure dropping to normal and dyspnea disappearing in a few hours There

(2) C d M A J 65 30 306 O tob r 1951

hour whenever blood pressure rose above 140/90 mm Hg dosage was repeated In the occasional patient with no de crease in arterial pressure an hour after initial 0 75 unit dose it was increased to 0 9 unit and if necessary to 1 05 units after another hour until effective dosage was established Nausea or vomiting was immediately treated with 50 mg pentobarbital sodium intravenously

In 17 moderate to severe pre eclampsia cases hypertension and toxemia symptoms were quickly controlled with vergitryl In mild pre eclampsia results were similar Of 15 patients with essential hypertension and superimposed toxemia blood pressure dropped to 140/10 mm Hg or less and signs and symptoms cleared Of 46 patients with early postpartum eleva tion of blood pressure 44 responded promptly with reduction of arterial pressure to normal There was simultaneous clin ical improvement with edema albuminuria and retinal angio spasm subsiding in most nonconvulsive patients The drug could be repeated hourly if necessary to maintain the hypo tensive effect but ordinarily the interval between doses was three to four hours No severe toxic reactions were seen only 11% of patients were nauseated and vomited There was no maternal or fetal mortality

In convulsive or eclamptic toxemias the drug was given intravenously for immediate effect In eight patients convul sions were promptly controlled and blood pressure decreased A living fetus was obtained in seven cases Moderate nausea and vomiting always occurred but could be controlled with pentobarbital sodium intravenously There was no maternal mortality

Essential Hypertension with Superimposed Pre-eclampsia Walter S Jones[5] (Providence R I Lying in Hosp) reviews 51 840 deliveries in 10 years (1939-48) Toxic cases occurred 1 533 times in 1 234 women (2 96%)

Benign hypertension in pregnancy is characterized by initial systolic pressure between 140 and 160 mm Hg usually with a slight fall in the mid trimester a transient rise during labor and return to prepregnancy levels after delivery Ab normal urinary findings are minimal and weekly weight gain is steady

With mild pre eclampsia blood pressure is normal until

(5) Am J Ob t & Gy 6 387 395 A gu t 1951

was given in four divided daily doses after meals and at bed time Tincture of belladonna or dramamine* was used to prevent or reduce nausea or vomiting both frequent in this series The same conventional methods for management of hypertension were used during the control and treatment periods

The series could be divided into three groups on the basis of response to medication Group I (five patients) had a blood pressure drop of over 20 mm Hg systolic and 10 mm Hg diastolic on daily total doses of 3 8 mg There were no ECG and heart size changes Group II (12 patients) received 2 6 mg daily without effect on blood pressure Dosage could not be increased because of nausea and vomiting Group III (eight patients) could not be given satisfactory treatment because of severe nausea and vomiting at dosages of less than 2 mg daily

One patient had a drop of blood pressure from an average of 180/125 mm Hg (control) to 115/85 mm Hg on 4 mg anatensol (Squibb) daily However after three months on the same dose blood pressure gradually rose to 170/110 mm despite a dosage increase to 7 mg daily Another patient on 8 mg of anatensol daily had a sustained fall of pressures lasting four months On placebo medication blood pressure immediately rose

It is concluded that even a highly purified extract containing two alkaloids of veratrum viride causes only an occasional sustained hypotensive response whereas in most instances nausea and vomiting prevent continued use of the drug without affecting the blood pressure

Clinical Evaluation of Vergitryl, New, Highly Purified Extract of Veratrum Viride Frank A Finnerty Jr and Edward D Freis[4] (Georgetown Univ) evaluated vergitryl in management of toxemias of pregnancy

Preliminary observations indicate that 95% of toxemic patients have definite blood pressure decrease with minimal side effects after 0 75 unit of vergitryl intramuscularly This circumvents need to titrate each patient separately as in continuous intravenous administration of crude extracts All nonconvulsive patients were given this dosage initially The drug was mixed with 1 cc of 1% procaine to prevent local pain Blood pressure and pulse rate were recorded every half

(4) M A D t ct f C lumb a 21 75 76 Feb ry 195

arterial pressure Diet built around salt free milk potatoes (especially baked) oleomargarine and sugar provides not only adequate calories but a satisfying variety of reasonably priced foods Adequate comparisons between rice and low sodium diet have shown that their efficiency depends chiefly on sodium restriction Resins are adjuvants only not substitutes for sodium poor diets Whether vegetable fat as well as cholesterol and animal fat should be reduced in the diet is still undecided

There is no way to predict which patient will benefit by surgery or in what degree Patients with malignant hypertension hypertensive heart disease and renal hypertension may do well Sympathectomy is resorted to when the progress of blood vessel disease is objectively demonstrable over months or years and medical management has been unsuccessful or impractical Total adrenalectomy is purely experimental

Potassium thiocyanate has one chief use—control of intractable hypertensive headache It may be given by vein at first and orally thereafter Headache present for months often disappears immediately and does not return as long as the blood thiocyanate level is kept at 3 6 mg /100 cc The drug must never be used without control of blood levels Various useful hypotensive drugs may give even better results in combination with each other and with a salt poor diet Individual susceptibility is pronounced the minimal dose of pentamethonium required to produce a fall of 40 50 mm Hg systolic pressure varying from 5 to 150 mg subcutaneously Hexamethonium is given by mouth in small doses gradually increased to 500 mg four to six times a day Nitroprusside and 1 hydrazinophthalazine have given encouraging results The veratrum alkaloids and dibenamine* are not effective Sedation is not used routinely but phenobarbital or mixtures of chloral hydrate and potassium bromide promote daytime relaxation without too much sleepiness Propylthiouracil 200 mg four times a day may help excessively anxious patients

Within a few weeks or months malignant hypertension may progress from a possibly reversible to a surely terminal stage Resolute and prompt decisions are vital Several choices are open Drastic low sodium or rice diet is the simplest but only about a quarter of the patients respond and many respond too slowly and precious time may be lost and with it

the last few weeks before term Increase in weekly weight gain is usually the first warning sign with this occult edema albuminuria may appear Usually hypertension follows

With pre eclampsia in a patient with established mild hypertension the clinical picture is practically a superimposition of the separate patterns of the two diseases with the resulting pattern analogous to that of severe pre eclampsia with pronounced weight gain albuminuria and systolic pressure over 160 mm (20 30 mm more than basal levels) The serious obstetric accidents that may occur are those of severe pre eclampsia

Of 203 women with mild hypertension 73 (36%) had pre eclampsia The earlier the pre eclampsia appeared the worse the prognosis Evidence of impending toxemia by the 32d week or appearance of any sign before the 36th week suggests that the pre eclampsia will be severe for less than half the serious complications occurred after the 36th week

Failure of excessive weight gain does not necessarily exclude pre eclampsia However any such weight gain should always be viewed with alarm

Separation of the placenta occurred in 299 cases (0 6%) of the total group 40% in toxic patients Eclampsia was seen in 0 18% of the total group but in 6 2% of the toxic patients Fetal loss was 13 7% among all toxic patients 13 3% among all hypertensives and 21 9% among those with superimposed eclampsia Of the toxic patients 19 (1 24%) died and among those with superimposed pre eclampsia 5 (6 85%) died

Essential or benign hypertension is a dangerous disease in pregnancy causing 14 times the normal incidence of pre eclampsia 10 times the incidence of toxic separation of the placenta 20 times the chance of cerebral hemorrhage and convulsive phenomena one third the chance of obtaining a live baby and 35 times the normal risk of maternal death

Treatment of Essential and Malignant Hypertension is discussed by Irvine H Page[6] (Cleveland Clinic) In overweight hypertensive patients total caloric intake should be reduced About a quarter of the patients respond satisfactorily to salt restriction Without rigid control to maintain a diet containing less than 200 mg sodium is impractical It is doubtful that diets with more than 500 mg sodium affect

(6) J A M A 147 1311 1318 Dec. 1 1951

operation (10% of one gland and 5% of the other were left in situ) They require supportive treatment one of 3 mg cortisone daily the other of 25 mg cortisone and 1 mg desoxycorticosterone acetate orally With careful regulation of cortisone dosage blood pressure has been kept normal and congestive heart failure relieved and specific cardiac medications are no longer needed In a third patient with similar amounts of adrenal tissue left in situ and no supportive treatment required immediate results were excellent but seven months later hypertension was again developing However headaches had been completely relieved The other patients with less adrenal tissue removed had varied and inconstant results but had some temporary reduction of hypertension and symptomatic improvement In one patient not improved by a Peet type sympathectomy a 90% subtotal adrenalectomy although causing only small changes in blood pressure completely relieved congestive heart failure

Following these experiences six patients were treated by leaving in situ a small fragment of adrenal (less than 1 cm in any diameter) sectioning of the splanchnic nerves on both sides and removal of paravertebral ganglions from the twelfth thoracic through the second lumbar segment In five early postoperative results were excellent Blood pressure did not respond in the sixth who however showed no adrenal insufficiency Two patients with advanced renal disease who had adrenalectomy only had marked decrease in blood pressure in the few months since the operation Four others were operated on too recently for results to be significant There was one operative death

The authors conclude that the combination of subtotal (90-95%) adrenalectomy and sympathectomy has given promising preliminary results (Replacement therapy with cortisone DCA and salt has not been a major problem with careful supervision) Furthermore if this combination of surgical treatment proves successful eventual medical treatment of hypertension becomes more likely it would point toward the medical control of the sympathetic nervous system activity and the depression of adrenal cortical function

Symptomatic Value of "Sign of Prethrombosis Observed in Retinal Vessels in Arterial Hypertension Compression of

the possibility of other therapeutic trials When the vascular disease is not advancing rapidly, diet should be tried The daily sodium content should be 200 mg or less if there is azotemia diet should also be low in protein Sympathectomy if done at all is indicated only in young patients early in the disease

Pyrogen the treatment of choice is given as an infusion in 200 cc saline in sufficient amounts to raise the temperature daily to 101 or 102 F Thereafter dose is determined by the temperature response of the previous day The only necessary criterion for selection is that renal function not be excessively low Treatment given six days a week must be prolonged until the patient receives no further benefit (three to four months) After treatment is stopped arterial pressure may rise almost to pretreatment level but even after several years the malignant syndrome has not returned

Observations on Results of Subtotal Adrenalectomy in Treatment of Severe, Otherwise Intractable Hypertension and Their Bearing on Mechanism by Which Hypertension Is Maintained Charles C Wolferth William A Jeffers Francis D W Lukens Harold A Zintel and Joseph H Hafkenschiel[7] (Univ of Pennsylvania) observed 23 patients 11 earlier patients 8 of whom had survived at least five months and 12 recent patients of whom 11 had survived at least one to three months All had severe hypertension unresponsive to medical treatment and unlikely to respond to sympathetic surgery

In 16 patients treated before the study reported here one adrenal gland had been removed during the second stage of thoracolumbar sympathectomy Some had been followed for almost two years after the operation but the cases are too few and the period of follow up too short to state whether unilateral adrenalectomy has improved the results of thoracolumbar sympathectomy alone There has been no evidence of adrenal insufficiency in this group

Subtotal adrenalectomy alone was performed on nine patients Three died one of pneumonia and adrenal insufficiency in the immediate postoperative period and two of recurrence of cerebral vascular seizures within two months Two of the six survivors had excellent results five and eight months after

(7) A I t Med 35 8 18 J ly 1951

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(7) A n I t M d 35 8 18 July 1951

patients observed with hypertension for 5 12 years PAH clearance was normal When PAH clearance is decreased focal ischemia may be the cause

Frank envisages the following sequence of renal blood flow changes At first flow is maintained despite renal arterial narrowing by the increased blood pressure Later despite further rise in arterial blood pressure this compensation does not insure normal flow But with constriction of the vas efferens glomerular filtration rate is kept within normal limits Still later this decreases also although relatively less than tubular clearance

Malignant hypertension—According to Frank[1] typical signs of this condition are severe diastolic hypertension increased intracranial pressure and progressive decrease in renal blood flow At first the decreased flow is probably functional being due to generalized vasoconstriction especially of the vasa efferentia Later there is severe anatomic damage typified by endarteritis of the small arteries and arteriolosclerosis necrotic changes and perivascular granulomas The severe intimal proliferation is thought to cause renal parenchymal atrophy and insufficiency Even with high diastolic pressures glomerular filtrate may be normal but fundoscopy shows papilledema and arteriolar narrowing In the early stages urine is normal but later hyposthenuria and ultimately isosthenuria develop

Malignant hypertension is associated with diabetic glomerulosclerosis the renal form of periarteritis nodosa and lead hypertension Periarteritis nodosa may cause the hypertension which develops in the absence of previous essential hypertension and takes a rapid relentless course of short duration

Eclampsia may be related to the eclamptic pseudouremia of acute glomerulonephritis A placental poison may be responsible by causing renal arterial spasms which according to the Trueta mechanism lead to cortical ischemia Essential hypertension predisposes to development of eclampsia and permanent hypertension probably makes it more likely

Antidiuretic hormone may play an important role in the pathogenesis of malignant hypertension especially since it also has a vasoconstrictor effect

(1) I t b I C trib Cl Sc 1 111 136 M h 1951

a vein by a crossing artery is the principal cause of venous thrombosis according to Paul Bonnet[8] (Lyon) With pressure by a sclerotic artery the vein appears compressed dark and tortuous where the artery crosses it As the vein walls alter and transudation of venous blood begins examination may disclose small hemorrhagic suffusions and exudates a white halo inflammatory in appearance around the vein above and below the arteriovenous crossing or a white border outlining the artery near the crossing These retinal manifestations indicating hindrance to venous circulation above the artery and suggesting eventual thrombosis are designated the sign of prethrombosis Thrombosis may follow quickly or may not appear for several years

Massive hemorrhage above the arteriovenous crossing usually occurs only when the sign of prethrombosis appears on a temporal branch of the central vein near the papilla When it appears at the peripheral arteriovenous crossings development is somewhat different Instead of massive spread small hemorrhagic suffusions appear above the crossing and extend toward the region of the macula (when they come from the superior temporal vein) disturbing central vision They then disappear without leaving a trace The small successive hemorrhages apparently enable the vein to adapt itself to the slow process of compression anastomosis takes place and newly formed vessels are sometimes seen between the vein segments on either side of the arteriovenous crossing Whether the vein undergoes adaptation or not the sign of prethrombosis indicates that the involved artery is sclerosed The sign has therefore real diagnostic value indicating a form of hypertension linked to arteriosclerosis

Present Day Views on Essential Hypertension—*Renal function in essential hypertension*—According to E Frank[9] there is general agreement that results of renal function tests including renal clearance may be within normal limits even in essential hypertension of long duration In the early stages total renal blood flow is normal But ultimately despite normal filtration rate para amino hippuric acid (PAH) clearance is decreased In some cases PAH clearance is normal though maximal tubular mass is already impaired In several

(8) A h opht 11 12 34 1951
(9) I t b l Co t b Cl n S 1 101 110 Ma h 19

or pulmonary embolus The rarity of pulmonary edema strongly suggested that it was actually prevented by this management Although some patients had angina pectoris only one had severe pain simulating a recurrence of thrombosis but the ECG and laboratory tests failed to corroborate it Most encouraging were continued sense of well being and high morale especially apparent in those experiencing a second or third occlusion When patients were permitted to walk there was no collapse dizziness or weakness

Some mortality is to be expected in myocardial infarction irrespective of treatment choice Immediate mortality is enhanced by advanced age paroxysmal arrhythmias heart block shock and congestive heart failure various combinations of which appeared in the seven who died The chair treatment cannot be held accountable for these deaths

Coronary Disease Clinical Pathologic Correlations and Physiology According to Herrman L Blumgart[3] (Beth Israel Hosp Boston) the coronary arteries are functionally end arteries in the normal heart Watery injections reveal anatomic fine anastomotic communications between the coronary arteries measuring less than 40 μ but they have limited functional significance in obviating the effects of sudden coronary narrowing or occlusion When colored radiopaque lead phosphate agar masses were injected into the three main coronary arteries of over 200 normal hearts (Schlesinger technic) there was no intermixture of color Since the lead agar suspension penetrates regularly only as far as arterioles 10-40 μ or more in diameter larger collateral pathways seem lacking in normal hearts Even in patients aged 70 or more who had normal coronary arteries no intercoronary anastomotic vessels were seen In about 40 per cent of all patients past 40 who died of noncardiac causes and had no manifestation of heart disease complete occlusion or considerable narrowing of one or more coronary arteries was seen The myocardium was usually normal on gross and microscopic examinations and often ECG s were normal This apparent inconsistency was dispelled by demonstration of the larger than normal collateral channels which by passed the obstructions or supplied the myocardium distal to the areas of narrowing or occlusion from neighboring unoccluded coronary arteries Al

(3) B ll N w Y k Acad Med 27 693 710 Dec mbe 1951

[There i rather strong evidence that some substance having an anti diuretic action is present in persons with congestive failure whether or not hypertension is present It has not been demon trated that this sub stance is of pituitary origin or that the posterior pituitary secretion plays a significant role in the pathogenesis of any type of clinical hypertension —Ed]

CORONARY ARTERY DISEASE

"Chair" Treatment of Acute Coronary Thrombosis was used by Samuel A Levine and Bernard Lown[2] (Harvard Univ) in 65 patients in whom this condition was definitely established Most of them were helped out of bed during the first two days and placed in a comfortable mobile chair until they were tired The goal was to have them out of bed as much of the day as was comfortable Some were up most of the day from the beginning of illness the majority were out of bed for one to two hours the first day and for increasing intervals thereafter Continued shock marked debility or concomitant cerebrovascular accidents were contraindications high fever severe pain friction rub diastolic gallop heart block cardiac arrhythmia or need for oxygen were not Nearly all patients fed themselves and used the bedside commode or had toilet privileges Anticoagulants were given all but nine Except for elevation of the bed headposts by 8 9 in blocks and consistent use of Ace bandages on the lower extremities they received routine coronary care A few steps were allowed by the end of the third week and hospitalization was maintained for about four weeks

One patient was out of bed the eighth and one the ninth day all others were in a chair within the first week 83% within the first three day Twenty four cases were uneventful (no complications or uninterrupted recoveries) In 20 re sults were good This group in addition to occlusion had paroxysmal rapid heart action shock or pulmonary edema and even so had a smooth course In 10 critically or termi nally ill patients with one or more of these complications start of recovery coincided directly with their being placed in a chair Seven of the 65 patients died

The few complications that occurred were not attribut able to the chair treatment There was no thrombophlebitis

(2) Tr A Am Phys ans 64 316 3 7 1951

one plane and a roentgenogram was made in order to study distribution and size of the vessels This method was supple mented by dissection of the vessels and microscopic study when indicated Hearts weighing over 350 Gm were consid ered hypertrophied Of 1 011 unselected autopsies adequate clinical data were available for 905

Of the 905 patients 177 had angina pectoris for at least a month preceding death As a control group 671 patients with out cardiac pain were studied All patients with angina pectoris had coronary arteriosclerosis arterial hypertension (at least 150/90 mm Hg) or valvular heart disease alone or in com bination Multiple causes were present in 75% and coronary artery disease in 90% Almost two thirds of the hearts showed old occlusions of the coronary arteries (average three occlu sions/heart) Only 16% of the patients with anginal pain had coronary artery disease without other cardiac conditions Slight coronary narrowing per se did not seem sufficient for production of angina In some hearts all three main stems were occluded in others one or both of the main arteries Occasionally only moderate to severe narrowing without oc clusion was found Even with good anastomotic circulation the margin of safety is small so that emotional or physical exertion anemia infection thyrotoxicosis or tachycardia may cause angina pectoris and its pathologic counterpart myo cardial fibrosis Even slight coronary narrowing may produce angina if contributory causes are present such as extensive pulmonary disease

A case of angina due to mitral stenosis and cardiac hyper trophy without coronary artery disease was seen but this is quite rare Increased anastomoses are more common with coronary artery disease than with valvular disease or myo cardial hypertrophy

Over half the patients with coronary occlusion had angina but only 3% of those with hypertension 16% with valvular disease and 5% with coronary narrowing only The greater the degree of coronary obstruction the greater the incidence of angina

Ratio of males to females was 2 5 1 (control group 1 4 1) Age at death was 21 84 All seven patients who died before age 40 had valvular disease When coronary artery disease was the only cause of angina it was never observed before

though serious damage may be avoided by development of such collateral circulation coronary reserve was presumably reduced

Severe arteriosclerotic coronary narrowings and occlusions were seen in 90% of the hearts of patients with angina pectoris *in most at least one main coronary artery or a* primary branch was occluded In angina pectoris coronary failure and acute myocardial infarction the underlying mechanism *seems to be a relative disproportion between* requirements of the heart for blood and the supply through the coronary arteries Resulting myocardial changes depend solely *on the extent and duration of the relative ischemia not* on the manner of production Immediate and complete bed rest sedation reduction of excessively high cardiac rates and other measures designed to reduce the work of the heart in the presence of prolonged cardiac pain is essential in limiting the extent of myocardial necrosis or even preventing its development Such a regimen also allows development of a more adequate collateral circulation Similar considerations would seemingly apply when angina pectoris appears suddenly or when the frequency or intensity of the attacks suddenly increases

[As is apparent from the preceding articles there is considerable difference of opinion about the use of complete bed rest The cardiac work, which is roughly the product of output and blood pressure tends to be less in the sitting than in the recumbent position Patients who have angina at rest in the absence of psychic stress are much more apt to have it when recumbent than when sitting The editor disagrees with Blumgart s recommendation of complete bed rest and is more inclined to recommend management along the lines indicated in the preceding article (see also Levine s article this YEAR BOOK p 476) Patients with recurrent attacks of angina at rest are often benefited by small doses of nitroglycerin at frequent intervals to prevent pain *It is possible* but unproved that such management also tends to promote collateral circulation —Ed]

Angina Pectoris Clinical and Pathologic Correlation Paul M Zoll Stanford Wessler and Herrman L Blumgart[4] (Boston) *investigated the roles of hypertension* valvular and coronary heart disease and of intercoronary collateral circulation and the importance of extracardiac factors in production of angina pectoris Under pressure radiopaque material was injected into both coronary arteries at their ostia The heart was then opened so that the major coronary arteries lay in

(4) Am J M d 11 331 357 Sept mber 1951

(5) gallop rhythm (6) congestive heart failure (7) auricular fibrillation or flutter ventricular tachycardia or intraventricular block (8) diabetic acidosis pronounced obesity previous pulmonary embolism varicosities in the lower extremities thrombophlebitis (past or present) or other states predisposing to thrombosis Of 623 patients studied aged 30 88 (mean 58 1) 473 were male History of hypertension was found in 28% of men and 47% of women In classifying patients as good or poor risk only facts in the history and physical examination available the first day of hospitalization were considered After classification clinical course and subsequent outcome were studied

Results are summarized in the table Of good risk patients 80% were hospitalized the day of attack indicating that low mortality was not the result of distortion from de

MORTALITY RATE AND INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS

	C ses	M AL TY		Em o N	
		N	%	N	%
Total	623	247	39 6	44	7 1
Good risk	285	10	3 5	2	7
Poor risk	338	237	70 1	42	12 4

layed hospitalization Of 10 deaths among the good risk cases 5 occurred within 48 hours of hospitalization before dicumarol® could have had significant effect of the other 5 deaths 2 were from causes independent of the cardiovascular system 1 from recurrent myocardial infarction and 2 from undetermined causes If it is assumed that the last three patients might have survived with dicumarol® therapy (an unconfirmed assumption) theoretically preventable mortality for the 285 good risk patients would be 1 1% A similar figure (0 98%) for theoretically avoidable deaths was noted in a previous study Only two good risk patients (0 7%) had thromboembolism

Combining this series with previous studies there were 1 047 patients with 3 1% mortality for 489 good risk cases classified according to the same criteria and an 0 8% incidence of thromboembolic complications for the same group Preventable mortality for the selected cases under dicumarol® therapy could not have exceeded 1 0% Since such slight benefit would probably be nullified or even overbalanced by complications induced by the drug it should be reserved for more

age 40 Duration of life after onset of anginal symptoms was 1 month to 19 years (average 4 2 years) A third of all patients died within one year after the first symptoms appeared and almost half were dead in two years Cause of death was related to the heart disease in 60% Congestive heart disease had a worse prognosis in coronary artery disease than angina whereas angina is the more serious symptom in valvular heart disease

Exact dates of onset were known for 50 patients with angina and infarction Intercurrent infarction did not make the prognosis worse Recovery from a single episode of myocardial infarction has the same significance as a history of angina and the same effect on life expectancy

Grossly dissectible intercoronary anastomoses were found in 17% of the hearts with old occlusions but never in normal ones Although such collateral channels may prevent myocardial infarction they do not prevent reduction of coronary reserve due to coronary narrowin Since coronary obstruction and myocardial fibrosis are so often found when angina has been present during life myocardial ischemia is believed to be the cause of the symptom Any factor which causes a discrepancy between demand and supply of coronary blood flow may cause an attack Only rarely if ever is angina produced by extracardiac factors without the presence of underlying coronary valvular or hypertensive heart disease Thus diagnosis of angina pectoris almost always implies organic heart disease

[In patients with disorders such as chronic pulmonary fibrosis and mitral stenosis which produce pulmonary hypertension the diagnosis of angina pectoris should be made with great caution There is strong evidence that pulmonary hypertension may mimic angina pectoris very closely (Circulation 5 1 1952) —Ed]

Indications for Bishydroxycoumarin (Dicumarol®) in Acute Myocardial Infarction Henry I Russek Burton L Zohman Alexander A Doerner Allen S Russek and LaVere G White[5] (U S P H S Hosp Staten Island N Y) selected from records of consecutive patients with myocardial infarction hospitalized in five years those with no signs unfavorable to recovery within the first 24 hours Such signs included (1) previous myocardial infarction (2) intractable pain (3) extreme or persistent shock (4) significant heart enlargement

(5) C cul t o 5 07 711 M y 1952

(5) gallop rhythm (6) congestive heart failure (7) auricular fibrillation or flutter ventricular tachycardia or intraventricu lar block (8) diabetic acidosis pronounced obesity previous pulmonary embolism varicosities in the lower extremities thrombophlebitis (past or present) or other states predispos ing to thrombosis Of 623 patients studied aged 30 88 (mean 58 1) *473 were male History of hypertension was found in* 28% of men and 47% of women In classifying patients as good or poor risk only facts in the history and physical ex amination available the first day of hospitalization were con sidered After classification clinical course and subsequent outcome were studied

Results are summarized in the table Of good risk pa tients 80% were hospitalized the day of attack indicating that low mortality was not the result of distortion from de

MORTALITY RATE AND INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS

	C ses	Mo tal ty		Em r n	
		N	%	N	%
Total	623	247	39 6	44	7 1
Good risk	285	10	3 5	2	7
Poor risk	338	237	70 1	4?	12 4

layed hospitalization Of 10 deaths among the good risk cases 5 occurred within 48 hours of hospitalization before dicu marol® could have had significant effect of the other 5 deaths 2 were from causes independent of the cardiovascular system 1 from recurrent myocardial infarction and 2 from unde termined causes If it is assumed that the last three patients might have survived with dicumarol® therapy (an uncon firmed assumption) theoretically preventable mortality for the 285 good risk patients would be 1 1% A similar figure (0 98%) for theoretically avoidable deaths was noted in a previous study Only two good risk patients (0 7%) had thromboembolism

Combining this series with previous studies there were 1 047 patients with 3 1% mortality for 489 good risk cases classified according to the same criteria and an 0 8% inci dence of thromboembolic complications for the same group Preventable mortality for the selected cases under dicumarol® therapy could not have exceeded 1 0% Since such slight bene fit would probably be nullified or even overbalanced by com plications induced by the drug it should be reserved for more

serious instances of acute myocardial infarction in which frequency of thromboembolism justifies the risk

Relief of Pain in Acute Myocardial Infarction by Procaine Block of Sympathetic Nerve Supply Carlos A Fish and Everett G Grantham[6] (Univ of Louisville) report a case

Physician 55 for over two years had had angina pectoris of effort relieved by nitroglycerin He was suddenly seized with an agonizing substernal pain and was hospitalized after nitroglycerin brought no relief The pain gradually intensified and various nar cotics even given intravenously produced no relief The pain also radiated down the left arm along the arterial blood supplies sub clavian axillary brachial radial and ulnar arteries but did not fol low the ulnar nerve After about 2½ hours a 1% procaine solution was injected in the stellate ganglion region through a supra clavicular approach and in a few seconds pain in the arm dis appeared as did the subpectoral then the substernal pain Within three minute he was comfortable Three hours later pain recurred and was relieved by stellate block In the next 36 hours 12 further injections were given after which all pain ceased

Electrocardiograms taken repeatedly from the time of admission showed the typical pattern and evolution of a recent posterior wall myocardial infarct Despite a stormy course complicated by auricular fibrillation congestive heart failure and intestinal bleeding presum ably due to anticoagulants the patient gradually improved and ulti mately returned to a limited practice He remained asymptomatic and required no medication

Stellate block should be tried when severe pain due to re cent myocardial infarction does not respond to the usual methods

Diet and Lipotropic Agents in Arteriosclerosis From a review of the literature Jack D Davidson[7] (Columbia Univ) concludes that in certain circumstances low cholesterol low fat diets can lower serum cholesterol levels The degree of dietary lipid restriction necessary to achieve this in some pa tients may preclude use of this regimen It is not established that maximal depression of serum cholesterol level obtainable by dietary measures will affect arteriosclerosis in man evi dence in animals suggests that a restricted lipid intake pro duces regression of induced arteriosclerotic lesions All data available indicate that despite individual positive reports there is no general agreement that choline and inositol have any specific influence on arteriosclerosis or the serum cholesterol

(6) A n Int Med 36 172 177 J u ry 1952
(7) Am J Med 11 736 745 Dec mber 1951

Reduction of Mortality Rate in Coronary Atherosclerosis by Low Cholesterol Low Fat Diet Lester M Morrison[8] (College of Med Evangelists) placed 50 alternate patients (42 male average age 60) with proved myocardial infarction on a 20 25 Gm fat (50 70 mg cholesterol) daily intake for three years 50 alternate patients (43 male average age 62) adhered to their customary cholesterol fat intake of 80 160 Gm fat daily (200 1 800 mg cholesterol) Mean weight at the outset of the *dietetically treated patients* was 166 lb for the men and 141 lb for the women After three years on the low fat diet mean weight was 145 lb for men and 124 lb for women Weights of the controls at the beginning and after three years were not significantly altered

Of the dietetically treated patients seven died three of recurrent myocardial infarction three of cardiac congestive failure and one of pneumonia Of the controls 15 died 7 of recurrent infarction 6 of cardiac congestive failure and 2 of acute cerebrovascular accidents All fractions of the serum lipids were greatly reduced in most patients after three years of dietetic treatment total serum lipid levels (mean) fell from 840 mg to 571 mg neutral fat fatty acids from 236 mg to 120 mg phospholipids from 292 mg to 231 mg and serum cholesterol from 312 mg to 220 mg Rapidity of the drop in serum levels was in the order given Many patients required one to two years on the low fat dietary regime before serum cholesterol levels fell A few showed no tendency to significant fall in serum cholesterol levels particularly in the early phases (under one to two years) Many patients who had angina pectoris on exertion before or immediately after recovery from acute coronary thrombosis noted that on the low fat diet *severity of anginal pain was reduced first then frequency of* attacks despite the same physical activity Many noted an increase in well being and capacity for work perhaps attributable in part to weight reduction and/or psychotherapeutic factors

Although a 50% decrease in mortality was suggestive statisticians found the series not amenable to strict analysis Preliminary observations with even lower fat intake i e 8 Gm daily indicated an even lower mortality rate

(8) Am H t J 4 538 545 O tobe 1951

"Giant Molecules" and Cholesterol in Relation to Atherosclerosis are discussed by Ancel Keys[9] (Univ of Minnesota) The Gofman group recently tried to establish a correlation between *occurrence of atherosclerosis and lipid bearing* substances in the serum characterized by their response to ultracentrifugation—the so called S_f 10 20 molecules (—10 to —20 Svedberg sedimentation units) or G substances

Arguments for the importance of the G particles in atherosclerosis are their higher concentrations in the serum of patients who have had a myocardial infarction than in that of *normal persons and also the significant correlation* between the concentration of the substances and the degree of atherosclerosis produced in rabbits by feeding cholesterol However Keys challenges the conclusions that values for G substances show a better *correlation* with atherosclerosis than total cholesterol values Gofman s data for both G and total cholesterol values in normal and infarcted groups overlap considerably *Actually total cholesterol measurements* separate the groups more sharply However neither determination affords sharp discrimination between the groups unless G and cholesterol values are extremely high and such values are found in only 10% of all cases of infarction

In experimentally produced aortic atherosclerosis correlation is equally good for total cholesterol and G substances However *it is not yet settled what relation* experimentally produced atherosclerosis has to the disease in man

One must guard against overinterpreting G and cholesterol values in patients with known myocardial infarctions and in normal persons The former group even assuming pronounced atherosclerosis may have no evidence of activity as far as lipid and cholesterol metabolism are concerned at the time the blood sample is taken The latter group on the other hand although clinically still normal may actually be developing atherosclerosis Only long follow up studies may settle these questions

Keys concludes that determination of G substances adds no information to that obtained by cholesterol measurements in predicting the degree or activity of atherosclerosis

Effect of Vegetable Fat Ingestion on Human Serum Cholesterol Concentration is reported by E A Hildreth S M

(9) B ll Joh s Hopk ns Ho p 88 473 483 M y 1951

Mellinkoff G W Blair and D M Hildreth[1] (Hosp of Univ of Pennsylvania) Three of the authors (healthy men) subjected themselves to the following strictly controlled diets for three to eight months (1) customary diet (2) diet with marked restriction of both fat and cholesterol and (3) diet low in cholesterol but with normal (vegetable) fat intake Total caloric intake was the same throughout Serum cholesterol values were determined twice weekly

In all three subjects reduction in dietary fat caused a pronounced fall in average serum cholesterol concentrations 217 170 mg/100 cc 287 241 mg 221 162 mg When fat intake was restored to normal but cholesterol intake was still restricted there was a rapid rise in serum cholesterol toward control values in two subjects but more gradual rise in the third

It is concluded that restriction of total fat rather than of cholesterol alone is the significant and determining factor in reduction of serum cholesterol

Principles of Low Fat Diet are discussed by E A Hildreth D M Hildreth and S M Mellinkoff (Univ of Pennsylvania) Restriction of total fat reduces serum cholesterol concentration even when the amount of dietary cholesterol is normal When a normal subject who had ingested 140 Gm fat daily was placed on a diet restricting total fat but containing 500 mg cholesterol serum cholesterol concentration fell about 60 mg /100 cc This and other evidence indicate that total fat content of the diet is more important in determining serum cholesterol concentration than amount of cholesterol ingested

The amount of fat restriction necessary varies in different people Serial determinations of serum cholesterol concentration show the effectiveness of the prescribed diet The authors usually start normocholesteremic patients on 25 30 Gm fat diets In a month or more if serum cholesterol concentration has not responded as desired the diet is further restricted In some cases usually in hypercholesteremic patients dietary fat had to be restricted to 10 Gm /day In some of these cases although serum cholesterol concentration could be reduced by 100 500 mg /100 cc by such diets normal values could not be reached Many textbooks even recent ones contain tables on

(1) C culat 3 641-646 M y 1951
(2) Ib d 4 899 904 Dec mbe 1951

fat content of foods which are out of date Reliable data can be found in the 1951 edition of *Food Values of Portions Commonly Used* by Bowes and Church (Philadelphia College Office Press)

From sample menus of the patient's diet as submitted by him, supplemented by inquiries about snacks one can readily determine his food habits and foods which must be limited For a diet containing 25 30 Gm fat daily, instructions might be as shown in the following examples integrated with an instruction sheet giving detailed information about foods to be avoided ways of making the diet palatable and how to substitute one food for another

EXAMPLE 1 —A few patients have no desire for butter or eggs. Therefore the diet will contain meat fish and poultry three servings (18 Gm fat) bread and cereal four slices of bread eggs, none beverages 1 qt powdered milk preparation (1 Gm) butter none salads 1 tablespoon dressing (6 Gm)

EXAMPLE 2 —Most people prefer more variety Therefore the diet will contain meat two servings (12 Gm fat) egg substitute (for meat when desired) bread and cereal three slices (3 Gm) beverages 1 2 qt powdered milk preparation or skim milk (1 Gm) butter 2 pats salad dressing only when substituted for the daily butter allowance

To prevent monotony the patient must be told how to change the menu within the limits of the fat restriction Since fresh and canned vegetables and fruits (other than avocados) plain sugar candies and fat free desserts can be used without restriction there is no reason for hunger or weight loss unless this is desired Foods to avoid fall in general into the following groups fried foods fatty cuts of meat cream whole milk and their products concentrated vegetable oils such as peanut butter shortening mayonnaise and similar substances avocados nuts olives and soybeans

Hypercholesteremia and Atheromatosis in Chicks on Restricted Diet Containing Cholesterol were investigated by S Rodbard C Bolene and L N Katz[3] (Michael Reese Hosp) because high caloric intake and obesity have long been thought implicated in the development of atherosclerosis Forty chicks divided into three groups were given restricted diets (about 60% of normal control) containing 8 2 or 0 25% cholesterol Control groups of 10 chicks received the same diets ad libitum Plasma cholesterol levels were determined

(3) Circulation 4 43 46 July 1951

often and incidence of atheromatosis in the thoracic aorta was measured when the birds were killed after 5 10 or 15 weeks

Weight gain of the chicks on the restricted diet averaged about two thirds of that of the control chicks However for the 0 25 and 2% cholesterol groups on restricted diets cholesterol taken/kg chick was about the same as that for the control groups Plasma cholesterol levels were about the same in all Degree and incidence of atheromatosis were similar for all chicks fed a cholesterol enriched mash regardless of whether total intake was limited if anything they were slightly greater in chicks on restricted diets containing cholesterol

Results suggest that obesity is not necessarily a factor in atherosclerosis Hypercholesteremia and atheromatosis are related to the amount of cholesterol ingested/kg body weight not to total caloric intake They may occur in the starved animal but be absent when there is high caloric but low cholesterol intake

[The foregoing articles indicate continued disagreement about the dietary management of coronary arteriosclerosis and other atheromatous states Each year the evidence that diet is important seems to become stronger However some believe that cholesterol per se is important Others hold that total fat is the offending factor while others believe that restriction of caloric intake constitutes the main dietary problem. Despite the many excellent investigations definitive answer must await long term studies of many hundred of well controlled patients Meanwhile it seems wise to restrict cholesterol and total fat intake of all subject with coronary disease and to restrict total calories except in patient already somewhat underweight —Ed]

Tetraethylammonium Chloride in Treatment of Coronary Artery Disease Irving Hirshleifer George Schwartz Howard J Fuerst and Arthur Fankhauser[4] (Kings County Hosp) report results of TEAC treatment of 23 patients with severe coronary insufficiency with or without myocardial infarction Intramuscular injections were used to avoid or reduce serious side effects such as rapid fall in blood pressure Initially 300 500 mg was given daily for three days Depending on response and side effects dosage was then individualized The intention was to increase each dose and spread the interval between administrations In most instances 200 900 mg was given weekly in one or two doses Maximal blood pressure drop was usually seen within 15 minutes after injection To avoid

(4) N w Y k J Med 52 575 579 M 1 1952

postural hypotension, patients were kept recumbent for 30 minutes

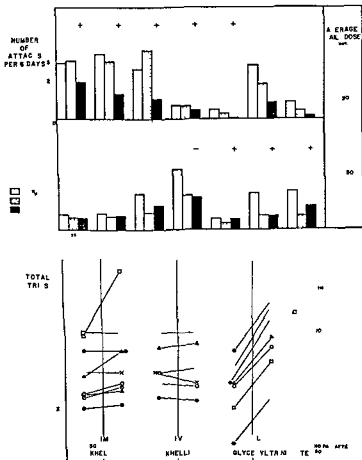
All patients had great relief from pain as evidenced by decreased number and severity of attacks and increased work capacity All were less dependent on nitroglycerin and some actually stopped using it Five had less marked S T segment shifts in the ECG and two had an improved response to an exercise tolerance test In five patients TEAC was given for precordial pain during an episode of acute myocardial infarction all experienced great relief

Improvement has been maintained for two to six months in nine patients after therapy was discontinued The other 14 still need the drug to remain free from pain

Clinical and Experimental Study of Use of Khellin in Treatment of Angina Pectoris is reported by Herbert N Hultgren H Schuyler Robertson and Leyland E Stevens[5] (Stanford Univ) Thirty patients who had 1 30 attacks of angina during ordinary daily activity were studied Diagnosis had been verified by careful study A blind test technic was used Each patient kept a daily record of the time of each attack the number of glyceryl trinitrate tablets used and any symptoms possibly due to the medication being given Control was established by not giving medication for the first week or two The patients were then given a numbered box containing either 50 mg tablets of khellin or identically appearing placebos Periods of placebo and khellin administration were alternated with periods during which a record was kept but no tablets given

Fourteen patients considered reliable observers were followed for a sufficient period Results are summarized in Figure 74 The 14 patients could be divided into two equal groups (1) those who had a distinct reduction in frequency of anginal attacks (30% or more) while receiving khellin as compared with periods of placebo administration and (2) those with no significant reduction (less than 25%) in attacks during khellin therapy Khellin seemed of some value in the angina However all patients apparently benefited had some toxic symptoms (indicated by plus signs in Fig 74) varying from mild malaise and anorexia to nausea and vomiting Because the effect of the medication on the patient s

[5] A M A 148 465 469 Feb 9 1952



F g 74 (top) —Eff t f kb ll g lly f q y f ang n 14 pa t t tud d by bl d te t t h

F g 75 (b ttom) —Eff t f kb ll g p t lly comp d w th ff ct f gly ryl t nt t g n rally p ty f ght p t t w th gina Cont l cap ty d ted t l ft f rt l l nd se p ty ft m d cat to th ght

(Cou t y f H ltg H N *et al* J A M A 148 465 469 F b 9 1952)

total activity was unknown more objective methods were used to evaluate the preparation

Exercise was performed using standard steps After a control period during which chest pain and ECG changes ap

peared the patient rested for 40 minutes after which the ECG returned to its pre exercise appearance A tablet of glyceryl trinitrate (0 4 mg) was then placed under the tongue Five minutes later exercise was performed in an identical manner Every patient studied showed a significant increase in exercise capacity (Fig 75) On subsequent days the study was repeated using single intramuscular (50 150 mg) or intravenous khellin injections (30-60 mg) Injections alone did not change the ECG Exercise was performed 15 20 minutes after intramuscular and 5 10 minutes after intravenous injections A consistent change in exercise capacity was no noted after either route (Fig 75) Daily intramuscular administration of khellin similarly failed to improve exercise capacity of five patients Intramuscular administration of 100-150 mg khellin had no effect on cardiac output pulmonary artery pressure or systemic arterial pressure in five patients with various circulatory disorders

Further clinical use of khellin appears of doubtful value but studies at higher dosage levels are indicated

Influence of Pentaerythritol Tetranitrate (Peritrate) on Acute and Chronic Coronary Insufficiency was studied by Travis Winsor and Patrick Humphreys[6] (Los Angeles) Chemically the drug belongs to the same group as nitroglycerin and mannitol hexanitrate Of 250 patients studied 125 had typical angina pectoris for at least five years They were aged 35 74 (average 56 5) 60% were male Each had been followed at least three years and had had some relief from acute anginal attack with nitroglycerin As controls 125 patients of similar age distribution with other diseases producing pain in and around the chest but without angina were studied Both groups kept a record of frequency intensity and duration of pain and number of nitroglycerin tablets used A control period of three months was followed by a test period of the same length Dosage of peritrate was 10 60 mg daily (average 29 3 mg) taken every four hours during waking hours

In 16% of the 125 patients with anginal attacks who took peritrate frequency of attacks was reduced 80 100% in 28 8% it was reduced 50 79% and in 33 6% it was reduced 20-49% Of the controls 96% showed no improvement

(6) A g l gy 3 1 15 F bru ry 195

In a subgroup of 31 patients with angina pectoris peritrate (30 mg daily) was compared in its effectiveness to reduce anginal attacks with no treatment placebos aminophyllin (9 gr daily) khellin (60 mg daily) and theocalcin® (1 5 Gm daily) Each patient had a test period of two months with each of the six plans of treatment Peritrate reduced attacks by an average of 78 4% whereas the other drugs gave the same results as no drugs or placebos In eight patients an average daily dose of 31 mg peritrate daily reduced the number of nitroglycerin tablets needed by an average of 73 9% over a placebo

The effects of peritrate and placebos on the ECG were studied in six patients before and after a standard exercise test Negative S T segment shifts seen in control records after exercise were greatly reduced by the drug In one patient S T segment changes on exercise were tested with peritrate papaverine ammivin aminophyllin nitroglycerin and no drug Peritrate was most effective in preventing these shifts being similar to nitroglycerin

Ten patients with angina were made to walk a 10% grade at 40 steps/minute until precordial pain occurred Peritrate (average dose of 36 5 mg daily) allowed them to take 50% more steps than did placebos

Side effects were infrequent and mild Headache and nausea usually disappeared on continuing the drug or were easily controlled Dermatitis required cessation of the drug in one instance Occasionally a patient had weakness palpitations abdominal gas and flushing Complete blood and urine examinations monthly for six months in 13 patients showed no significant changes

Peritrate in 10 mg doses three times daily before meals significantly improved precordial pain in 75% of the patients significantly reduced nitroglycerin requirement and increased exercise tolerance

Comparative Action of Penta Erythrol Tetranitrate and Other Coronary Vasodilators in Angina Pectoris was studied by P Dailheu Geoffroy[7] (Paris) in 258 patients Total daily dose of 60 mg penta erythrol tetranitrate equally divided into three portions was given before each meal for 10 of 14 days for a month Frequently alternate treatment with heavy

(7) I d H t J 198 206 S pt mb 1950

dosages of iodine and vitamin B was used Dosage of penta erythrol tetranitrate should be the same whether or not trinitrin is combined Trinitrin should only be used in resistant cases after other medications fail or when the electro clinical syndrome appears particularly acute

Little more than 33% of the patients improved with ordinary coronary vasodilators but over 80% showed good response to penta erythrol tetranitrate Complete failures were rare especially if trinitrin was added Sex and accompanying hypertension had little bearing on the results except that hypertensive women in menopause appeared to respond only to penta erythrol tetranitrate with trinitrin added The r e failures occurred in particularly resistant cases more often among the young and among those who had also shown no improvement after x ray therapy or infiltration of the stellate ganglion or periaortic plexus Greatest improvement was seen in those in the age when angina is most prevalent Sclerosis in the aged seemed not to hinder the action of penta erythrol tetranitrate actually young patients often respond less favorably

The advantage of penta erythrol tetranitrate over other coronary vasodilators rests in its greater efficiency and the longer duration of its effectiveness The patient is protected from renewed paroxysms for several hours and may even lead a fairly normal existence If limited exertion becomes necessary a precautionary dose of 10 mg taken one half hour in advance should be sufficient Should a spasm occur another equal dose will stop it and prevent recurrence for three to six hours Such practice would avoid the often harmful use of trinitrin

[Glyceryl trinitrate (nitroglycerin) is rarely harmful when used in proper dosage One awaits with interest comparative studies of the effect of penta erythrol tetranitrate three or four times daily and of glyceryl trinitrate (nitroglycerin) taken at shorter intervals such as every one to two hours In any case it appears that these compounds are much more active than the khellin derivatives —Ed]

Treatment of Shock in Recent Myocardial Infarction by Intra arterial Transfusion Earl N Silber Burton D Levin Gerald H Becker and Robert C Levy[8] (Michael Reese Hosp) report on nine patients in severe shock who had a history

(8) J A M A 147 16 6 16 9 Dec 2 1951

compatible with infarction and confirmed by electrocardiogram

PROCEDURE —The radial artery was delivered through a 3 5 cm longitudinal incision above the styloid process and cannulated so that the infusion was directed toward the heart Whole blood was used in seven cases because of its oxygen carrying capacity and to eliminate the danger of ischemic necrosis associated with use of other agents Although the total amount was intended to be 250 300 cc blood the theoretical capacity of the arterial tree much more was usually necessary to obtain the de ired clinical response In two cases pla ma was used because whole blood was not immediately available Despite a depressed sensorium the procedure always pro voked severe pain along the vessels of the arm particularly im mediately after transfusion was started Spasm of the collapsed ves sel in response to sudden distention by the blood infused under pres sure apparently caused the pain Liberal infiltration of 1% procaine solution at the infusion site was ineffective morphine was often necessary

In six of the nine cases blood pressure was 0 immedi ately before transfusion In the rest systolic pressure was 95 mm Hg or less In no case was pulse pressure greater than 30 mm Hg A significant initial restoration of blood pressure in eight cases was induced by 125 400 cc blood given in 10 20 minutes One patient moribund when transfusion was begun had no blood pressure response and died during the procedure In the seven cases a total of 250 500 cc whole blood was in fused over 20 30 minutes One hour after completion of the transfusion arterial pressure was higher than the initial pres sure response in four cases In one case systolic pressure fell slightly after an hour but subsequently rose again and was maintained In two others pressure fell after an hour from the initial level attained with transfusion In one case systolic pressure remained at the level of initial response Response was dramatic in four of these patients although two eventually died

Shoulder Hand Syndrome Following Myocardial Infarction Treatment by Procaine Block of Stellate Ganglion Daniel M Swan and John M McGowan[9] (Quincy Mass City Hosp) used an anterior approach usually as office and clinic procedures It is advisable that apparatus be on hand so that the patient may be kept on continuous artificial respiration

(9) J A M A 146 774 7 7 J 30 1951

with oxygen for one hour in case procaine enters the spinal canal Within 10 minutes procaine injection into the stellate ganglion completely relieved shoulder and arm pain and in one case constant pain in the precordial region More striking even than pain relief was the notable return of function in the muscles of the extremity which were in a chronic state of spasm so severe that it was difficult to raise the arm move the elbow or open and close the hand After the procaine block patients could open and close the hand with ease and move the arm at the shoulder and elbow One patient unable to raise his hand off the bed for three months could move the hand and arm with facility 10 minutes after the first block and after the third injection returned to work which involved handling precision instruments Another patient was more impressed with lessening of hand stiffness attributed to inability to relax the muscles After one treatment he could open and close the hand in a normal manner

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ELECTROCARDIOGRAPHY

Electrocardiographic Effects of Myocardial and Pericardial Injury are reviewed by Charles E Kossmann[1] (New York Univ) The most significant studies have been made by F N Wilson and associates who have investigated alterations in electrical behavior of the myocardium and defined the laws governing the effects of an electromotive force in a volume conductor The action potential of the (myocardial) cell is divided into five phases (1) depolarization (2) overshoot (3) complete activity (4) repolarization and (5) hyperpolarization Phases 2 and 5 can probably be disregarded in genesis of the ECG i e the QRST as seen clinically

Myocardial and pericardial injury may modify the basic processes (1) Complete anatomic and functional destruction of portions of the myocardium causes an initial negative potential a Q wave in certain leads (2) A current of injury during rest may produce a shift in the S T segment (3) Injury may prevent complete depolarization producing a demarcation potential (also seen in the ECG as an S T shift) (4) The second and third may combine to give additive effects

(1) Bull N w Y k A d M d. 28 61 89 F bruary 195

on the S T segments (this is probably the case in clinical myocardial infarction) (5) When recording is from intra cardiac electrodes a long negative potential may appear per haps due to hyperpolarization (6) Delay in rate of repolariza tion may cause changes in the T wave (change in ventricular gradient) Examples of most of these effects can also be ob tained in special circumstances from atrial electrograms Clinically evidence of atrial injury is found in atrial infarc tion occasionally associated with myocardial infarction

In myocardial infarction in the presence of left bundle branch block ECG diagnosis can occasionally be made de spite obscuring effects of the bundle branch block by T wave changes since repolarization is delayed locally Thus the ven tricular gradient is changed

Kossmann believes that although clinical and experimental studies of injured myocardium have shown high correlation discrepancies between ECG and anatomic observations may be due largely to the fact that considerable electrical disturb ances occur long before anatomic changes can be seen He presents ECG evidence of the manner in which an apical in farct can simulate exaggerate or nullify the ECG effects of diffuse pericarditis depending on its location If local peri carditis occurs over a transmural infarct it usually has no electrical effect because the myocardium under it is dead and thus electrically inert Electrical alternans of both QRS and T is often seen in acute pericarditis

Generalized Urticaria with Electrocardiographic Changes Simulating Myocardial Infarction. Robert F Foster and James D Layman Jr [2] (Providence Hosp Seattle) report a case

Woman 65 for two weeks had been treated with cincosal (sodium cinchophen 1 Gm sodium salicylate 1 Gm and sodium iodide 0 5 Gm in 20 cc) for arthritis No other treatment had been given Seven days before ho pitalization she noted itching of the scalp with rash at the hairline The same day she was vaccinated for smallpox and hives developed later over the entire body The day of hospitalization she suddenly experienced shortness of breath but had no chest pain or discomfort

Blood pressure and heart rate were normal There was moderate dyspnea Slight dulness and rales were noted in both posterior lung bases There was a generalized urticarial rash on the arms and trunk Complete blood count and urinalysis gave normal results A

(2) J A M A 148 03 05 J 19 195

to show any other cardiac disorder it seemed possible that anxiety incident to taking of the tracing caused the changes Therefore the ECG was repeated the next day after reassurance and 15 minutes of rest Surprisingly often this simple expedient led to a reversal of the RS T and T changes In 77 such patients the observed ECG changes (RS T segment depression and low or diphasic T waves in various leads) although slight were definite enough to make the ECG record abnormal or borderline The exact mechanism responsible for these ECG changes in anxiety and related functional disorder is not known A rapid heart rate as such is not the cause Since tachycardia per se is often accompanied by RS T and T changes all patients with heart rate over 100/minute were excluded Further the ECG changes often disappeared under rest and reassurance despite an unchanged heart rate There was no correlation between the observed T wave changes and exercise time of day or state of filling of the stomach

These functional ECG changes were seen often enough to warrant caution in interpreting minimal RS T and T changes In all such cases the ECG should be repeated after reassurance and 15 minutes of rest If the changes are thereby reversed anxiety should be suspected and further clinical studies made Final evaluation of an ECG should always depend on integration of the whole clinical picture

[The importance of the final statement cannot be overemphasized The overenthusiastic interpretation of minor electrocardiographic changes has been responsible for an untold amount of human suffering Minor ECG changes should be completely disregarded unless associated with unquestionable clinical evidence of cardiac disease Even such striking changes as bundle branch block may have no significance as indicated in the following article

Another common source of error is illustrated in Evans report (p 425) This is due to a failure to realize that the QRS complex in lead III and at times in aVF may be conspicuously influenced by breathing and position —Ed]

Bundle Branch Block without Significant Heart Disease Julius Wolfram[5] has found that bundle branch block especially on the right is seen in a large percentage of ECGs without definable anatomic or physiologic basis His study is based on 5 000 ECG s taken routinely at the cardiac clinic of the Veterans Administration Regional Office Dallas This clinic chiefly serves pension applicants and approximates a

(5) Am H a t J 41 656 666 M y 1951

routine private practice because through it passes a significant percentage of patients without cardiovascular disease

A careful history and complete examination including ECG and chest x ray were obtained in each case There were 52 instances of bundle branch block (17 left 35 right) in patients aged 25 70 over 20% being over 40 In two thirds of the patients this condition had not been previously diag nosed and only in 27% had it been diagnosed before aged 40

No evidence of organic heart disease was found in 74% of patients with right bundle branch block and 41% of those with the left variety In the absence of definite organic heart disease bundle branch block has an excellent prognosis and Wolfram warns against causing cardiac neuroses in pa tients whose only cardiac abnormality is this condition

Effect of Deep Inbreathing on Lead III of Electrocardio gram was studied by William Evans[6] in 200 healthy subjects and in 200 patients with heart disease Lead IIIR where R stands for respiration was compared with lead III In no in stance were the forms the same proving the unreliability of any lead that is built up in part from the electrical potential at the lower extremity Among common changes in lead IIIR in health were an increase in height of P R and T waves and shortening of the S wave compared with those in lead III A Q wave of 2 mm or under in lead III may persist in IIIR but a Q deeper than 2 mm was never found in IIIR Again a Q wave in lead III never deepened in IIIR or appeared in IIIR when absent in III An upright T wave in lead III never lessened in IIIR whereas a flat or inverted T wave rose significantly unless as rarely happened the heart was prevented from descending during deep inbreathing or even moved upward (paradoxical displacement) as in paralysis of the left dome of the diaphragm Depression of the S T seg ment in lead IIIR was not found in healthy subjects

In left ventricular preponderance from hypertension a depression of the T wave and S T segment was uncommon when cardiac pain was absent but in patients with pain such a change was invariable in lead IIIR this change in patients without pain was regarded as evidence of added coronary arterial disease In left ventricular preponderance from aortic

(6) B t H t J 13 457 466 O t b 1951

Value of Measurement of Q-T Interval in Series of Clinical Electrocardiograms F Dreyfuss and D Diengott[8] (Hadassah Rothschild Univ Hosp) examined 303 ECGs of ??3 subjects by measuring and averaging in leads I II III V_1 V_4 and V_6 the Q T interval by a slightly modified Bazett formula Altogether 144 Q T intervals were abnormal Electrocardiograms showing bundle branch block prolonged QRS auricular fibrillation or flutter and ECG s of patients on digitalis were excluded

Among the subjects were 66 with hypertensive cardiovascular disease 24 with arteriosclerotic heart disease 20 with rheumatic heart disease 17 with kidney disease 18 with gastrointestinal disease 12 with infections and from 4 to 7 each with cor pulmonale congenital heart disease subacute bacterial endocarditis possible heart disease liver disease hyperthyroidism neoplastic disease diabetes or metabolic and endocrine disease There were also 20 with no heart disease and 5 normal individuals

The patients with severe liver disease kidney disease (no severe hyperpotassemia) hypertensive cardiovascular disease metabolic and endocrine disorders and rheumatic heart disease as a group had corrected Q T intervals exceeding 0 420 second usually considered the upper limit of normal Highest average group value was in hypertensives (0 431 second)

Transient Q T prolongation occurred in several patient during acute episodes of coronary insufficiency Q T prolongation occurred in 58 otherwise normal ECG s

Although in itself an unspecific phenomenon the Q T interval on repeated determinations can be a sensitive indicator of the presence and course of cardiac impairment in certain conditions since it was abnormal in many cases in which the ECG was normal otherwise but heart damage was present

Q T Interval in Chronic Cor Pulmonale was evaluated by James K Alexander M Irene Ferrer Rejane M Harvey and Andre Cournand[9] (New York City) in 13 cases in view of its prolongation in many other types of heart disease All patients had chronic pulmonary disease with pulmonary insufficiency right ventricular enlargement or failure with pulmonary hypertension marked cyanosis with arterial desaturation

(8) Ca d log a 18 213 224 1951
(9) C culat on 3 733 737 M y 1951

and polycythemia and no other demonstrable cause for the heart disease All but four were in failure with hypervolemia and the elevated mean auricular and right ventricular end diastolic pressures characteristic of right ventricular failure None had received any cardiac drugs

The Q T interval and rate measurements were made in each of 12 or 14 ECG leads and averaged to calculate K in Bazett s formula In each case the average Q T duration for the given heart rate was below the upper limit of normal as was the K value in both patients with and without failure Similar measurements made in 14 cases of hypertensive cardio vascular and arteriosclerotic heart disease with left or right *heart failure showed abnormally prolonged Q T values in all* but 3 Calculated values for K were above the upper limits of normal in each case

It is suggested that measurements of the Q T interval may aid in differential diagnosis of pure chronic cor pulmonale and congestive heart failure due to other types of heart disease unless they coexist

New Method of Equating and Presenting Bipolar and Uni polar Extremity Leads of Electrocardiogram Advantages Gained in Visualization of Their Common Relationship to the Electric Field of the Heart John S Graettinger John M Packard and Ashton Graybiel[1] (U S Nav School of Aviation Medicine Pensacola Fla) point out that differences between bipolar and unipolar extremity leads lie only in their lead axes and the amplitude of their deflections (A cardiac vector derived from unipolar extremity leads is smaller by $\sqrt{3}$ than one derived from the bipolar leads) By drawing unipolar and bipolar lead axes into a hexaxial system each axis has 30 rotation from its neighboring axis (Fig 76) The angles between the leads are the same as in the Einthoven triangle To correct for different amplitudes of recording (unipolar leads being only 58% of the conventional projection of a vec tor on the lead) the unipolar leads are recorded to give a sensitivity of 1 mv =17 3 mm When augmented (Gold berger) unipolar leads are used the sensitivity is set at 1 mv =11 5 mm (2/3 $\sqrt{3}$) Each lead is then mounted at the end of its appropriate axis To complete the scheme the re verse of each lead is also mounted (by reversing its polarity)

(1) Am J M d 11 3 5 J ly 1951

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(8) C d l g a 18 213 224 1951
(9) C cul t n 3 733 737 My 1951

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(8) Cardiologia 18 213 224 1951
(9) Circulation 3 735 737 May 1951

and III (120) The direction of the approximate mean or instantaneous vector is determined easily from the angle of the axis of the lead with the tallest complex

This method allows quantitative and qualitative comparison between the various unipolar and bipolar leads and the

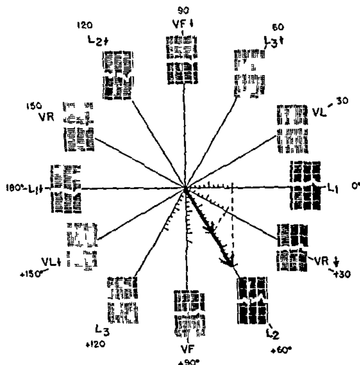


Fig 77 —B p l d pol t mty l ad d d w th on en l d w th d p la ty d mou t d t e d of f b l sy t m Scal f all d t l M f t m n f QRS i d d f om th u pola l d (11 6 m o lt d) d f om b pola l d (20 m lt ec d) (C t y of (tt g r J b r / Am J M d 11 3 25 J ly 1951)

viewing of the heart s electrical field along 12 axes in the frontal plane Mean vectors for P QRS and T can be determined by inspection and alterations in depolarization are easily estimated

Appraisal of Newer Electrocardiography Correlations in 150 Consecutive Autopsy Cases with pathologic findings was

(Fig 77) In this manner by simple inspection the relations of all leads can be determined as well as the mean manifest axis of the cardiac vector for QRS and T, since it will be at a right angle to the lead axis showing a transitional deflection Thus the direction of the mean or instantaneous cardiac vector and the general shape of the vectorcardiogram can be de

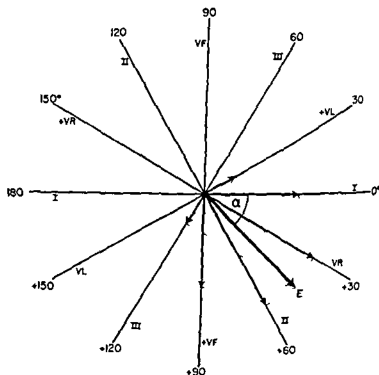


Fig 76—Projection of a cardiac vector (E) on of the limb leads. (Courtesy of Graettinger J S et al Am J Med 11 325 July 1951)

termined by inspection In addition by measuring the area of QRS and T in one lead and plotting it on the hexaxial system the ventricular gradient can be approximated

In simplified practice without changing the standardization six extremity leads are mounted from above down according to the angles of their axes with that of lead I aVL (—30) I (0) reversed aVR (30) II (60) aVF (90)

and III (120) The direction of the approximate mean or instantaneous vector is determined easily from the angle of the axis of the lead with the tallest complex

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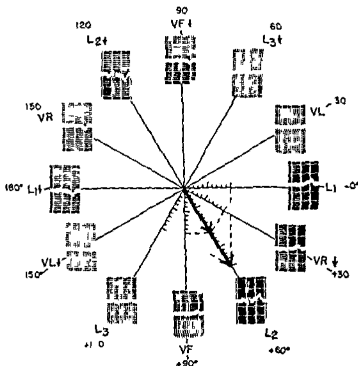


Fig 77 — B p la [illegible] (Courtesy of [illegible] et al Am J Med 11 325 July 1951)

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Appraisal of Newer Electrocardiography Correlations in 150 Consecutive Autopsy Cases with pathologic findings was

made by Harold D Levine and Edward Phillips[2] (Harvard Med School) At least one complete set of conventional leads and unipolar extremity and chest leads was made in each case. The ECG diagnosis of acute myocardial infarction was invariably correct However of all acute infarcts found at autopsy *only 75% were detected on ECG* Only 20% of old infarcts found at autopsy were correctly diagnosed on ECG Of those missed 50% showed left ventricular hypertrophy The ECG findings were not normal in any case of acute or old myocardial infarction Bundle branch block was seen in 7 of 12 instances of myocardial infarction involving the inter ventricular septum

The ECG diagnosis of left ventricular hypertrophy was invariably substantiated at autopsy However, other coexisting lesions such as right ventricular hypertrophy or myocardial infarction *were usually masked by the changes of left* ventricular hypertrophy An additional 12 patients with left ventricular hypertrophy did not show the typical ECG picture 7 of them had vertical heart positions and may not have been adequately explored electrically *Only 2 of 26* patients with combined ventricular hypertrophy were diagnosed by ECG In most cases in this group the ECG diagnosis of left ventricular hypertrophy was made The ECG diagnosis of right ventricular hypertrophy was substantiated in all eight cases Both patients with ECG s characteristic of right bundle-branch block and with a large secondary R wave (R) over the right ventricle had right ventricular hypertrophy at autopsy Diagnosis of acute cor pulmonale was confirmed in seven of eight patients in whom it was made by ECG It was missed on ECG in one other case

ECG findings were nonspecific and abnormal in 38 patients The chief anatomic diagnoses in this group were ventricular hypertrophy and coronary artery disease with or without infarction Ischemic toxic or chemical changes could explain the abnormal ECG s in seven cases Of 15 patients with normal ECG s 9 had apparently normal hearts 3 coronary artery disease without myocardial infarction 2 left ventricular hypertrophy and 1 unexplained edema of the heart muscle

Of 17 normal hearts at autopsy 9 showed normal ECG s 5 nonspecific changes 2 auriculoventricular block in 1 er

roneous diagnosis of old anterior myocardial infarction was made on the basis of a decreasing R wave in leads V_1 and V_2 and an absent R wave in lead V_3

ARRHYTHMIAS

Cardiac Arrhythmias Pathologic Physiology Diagnosis and Treatment are considered by George A Hellmuth[3] (Loyola Univ Chicago) Abnormal auricular rhythms arise from a local ectopic pacemaker and dominate the control of the heart beat Even auricular fibrillation and flutter may be of such origin rather than due to a circus mechanism of conduction suggested by Lewis

Arrhythmias have little functional cardiovascular effect unless they impair cardiac output and coronary flow Inci dence of thromboembolism may be increased in certain ar rhythmias especially auricular fibrillation and flutter

Bedside diagnosis of many disturbances of cardiac rhythm is often possible Cardiac rate is an important criterion supra ventricular tachycardias usually having a rate of 160 200 whereas the rate in sinus tachycardia is almost always lower Irregularity of the pulse occurs in premature contractions but may also be felt in atrioventricular block The irregular ir regularity of auricular fibrillation is usually easily diagnosed Auricular flutter especially with a 4 1 or 5 1 block is practi cally impossible to detect clinically Paroxysmal ventricular tachycardia is difficult to diagnose except from the history the rate is generally between 150 and 200 Carotid sinus pres sure often serves as a diagnostic test

The ECG is the final arbiter of the diagnosis of the ar rhythmias Attacks of paroxysmal auricular tachycardia in healthy subjects due to the Wolff Parkinson White syndrome are characterized by a short P R and a prolonged QRS inter val during regular rhythm

Many arrhythmias require no treatment This is true in most instances of premature contractions However quinidine sulfate (0 1 0 2 Gm) three times daily is usually effective If carotid sinus stimulation is not effective in terminating supra ventricular tachycardia vomiting agents may be helpful

(3) M Cl N th Am 36 3 20 J ry 195

Digitalis (in the usual doses) is of great value as is quinidine (0 2 0 6 Gm every two hours for four to six doses when the amount may be increased in steps of 0 1 0 2 Gm for successive doses) Quinidine is useful in maintenance doses to suppress an arrhythmia that has been stopped Mecholyl[3] (5 15 mg subcutaneously) may terminate a supraventricular tachycardia.

Digitalis is the drug of choice in auricular flutter Once fibrillation has been established quinidine may be used to restore sinus rhythm if desired If slowing of the ventricular rate is needed in auricular fibrillation digitalis is extremely effective Quinidine is used if conversion to normal rhythm is desired

Quinidine and procaine amide are most effective in paroxysmal ventricular tachycardia Procaine amide is given in doses of 0 25 or 0 5 Gm every two to five hours Maintenance dosage is 0 5 1 Gm every six hours Similar doses can be used to suppress ventricular premature systoles

Ventricular fibrillation if immediately recognized in surgical cases calls for rapid intravenous injection of 2% procaine amide hydrochloride application of a defibrillator and topical application of procaine In cases of cardiac standstill epinephrine injected into the heart (0 3 0 5 cc of a 1 1 000 solution in saline) may be effective

Complete atrioventricular block is best treated with the same dose of epinephrine in an emergency For less serious attacks and for maintenance ephedrine (15 30 mg orally three times a day) is given

With a better understanding of the underlying physiology more accurate diagnosis and a more rational use of the proper drugs cardiac arrhythmias can be more effectively treated than in the past

Auricular Flutter Results of a study of this mechanism in man and animals are described by Myron Prinzmetal Eliot Corday Robert W Oblath H E Kruger I C Brill Joshua Fields S Rexford Kennamer John A Osborne L Allen Smith Alvin L Sellers Walter Flieg and Eileen Finston[4] (Univ of California Los Angeles) All portions of both auricles were exposed in dogs and auricular flutter was produced by local application of aconitine or electric stimulation The motion throughout the fluttering auricles was clearly visual

(4) Am J Med 11 410 430 October 1951

ized by high speed cinematography Direct lead ECG s from all regions of the auricles including the hitherto unexplored body of the left auricle revealed the entire course of the flutter excitation wave Both contraction and excitation waves of auricular flutter arose from the ectopic focus and spread out ward through the auricles in all available directions simul taneously No circus movement was present The course of contraction and excitation waves of auricular flutter was simi lar to that of waves of auricular premature systole and parox ysmal tachycardia when the arrhythmias arose from the same site In man the excitation waves of spontaneous auricular flutter were traced by esophageal and precordial lead ECG s As in the experimental animal they arose at the ectopic focus and spread outward through both auricles simultaneously No circus movement was present Speed of the excitation wave in the human auricle was slower during auricular flutter than during normal sinus rhythm

The various ECG and therapeutic differences between auricular tachycardia and auricular flutter are related to dif ferences in auricular rate and do not indicate a fundamental difference in mechanism They represent the same fundamental disturbance in the auricles i e the discharge of impulses from an ectopic focus at a rate greater than the rate of discharge from the sinus node and lower than the fibrillation threshold Within this range the characteristics of tachycardia tend to appear at slower auricular rates whereas those of flutter occur most often at more rapid rates In man and experimental ani mal no sharp line of demarcation exists between tachycardia and flutter Quinidine converts both auricular flutter and auricular tachycardia to normal sinus rhythm by slowing the rate of discharge from the ectopic focus The concept that quinidine alters an excitable gap of a circus movement is erroneous

[On the basi of available ev dence knowledge concerning the man agement of ectop c rhythms may b ummarized as follows For preven tion and treatment of auricular tachycardia digital s is often the drug of choice but qu nidin is better in some patients For auricular flutter or auricular fibrillation of short duration qu n dine is likely to be the better drug although digitalis is occasionally preferable In ventricular tachy cardia procaine am de or quinidine should be u ed and d gitalis given only rarely For ventricular premature beats quinidine is often highly effective but fails completely in a sign ficant proport on of the pat ents These tentative conclusions will necessarily need to be mod fied on the basis of additi nal experience with these and newer drugs —Ed]

Auricular Fibrillation Myron Prinzmetal Robert Oblath Eliot Corday I C Brill H E Kruger L Allen Smith Joshua Fields Rexford Kennamer and John A Osborne[5] recorded contractile movements of fibrillating auricles by high speed color cinematography and electric activity by direct auricular leads in 2 patients and in over 35 dogs Motion of the fibrillating auricle was similar in man and dogs There were continuous chaotic rapid and asynchronous multitudes of areas of minute contractions and relaxations in all parts of the auricles simultaneously Microscopic (M) and large (L) activity heterorhythmic contractions and dilatations of microscopic muscle segments and relatively rhythmic waves traveling short distances along everchanging pathways were seen simultaneously in all contractile portions Movements of auricular fibrillation visible to the naked eye are due to the L waves which arise simultaneously at various sites in the auricles and travel various distances They are probably fusions of the M waves No evidence of circus movement could be found often the auricles did not contract at the same rate L waves did not turn around the venae cavae and M waves were always present which excludes the possibility of an excitable gap

Electrically auricular fibrillation was characterized by similar continuous rapid chaotic and asynchronous activity Direct auricular and esophageal leads showed minute (rapid irregular) and larger (less irregular slower) complexes which probably correspond to M and L mechanical waves Lack of synchronicity in simultaneously recorded leads from different sites was incompatible with a circus movement No isoelectric gap was seen

When auricles were stimulated by drugs auricular fibrillation was produced above a critical rate of stimulation (fibrillation threshold) The cinematograph showed that as the rate of ectopic discharge became ever more rapid contraction waves traveled over the auricles at slower speeds and auricular diastole was shortened until ectopic rhythm became so fast that recovery was too short and the chaotic activity of auricular fibrillation resulted Antifibrillatory drugs lowered the fibrillation threshold by depressing conduction the rate of discharge of a natural ectopic focus or both Quinidine is

(5) J A M A 146 1275 1281 Aug 4 1951

effective by depressing auricular conduction and the ectopic focus However when administered in experimental fibrillation conduction is actually improved while the ectopic focus is slowed L contractions become stronger whereas M waves decrease in rate and become more co ordinated as the fibrillation threshold is reached Electrically the change is shown by increased amplitude and decreased rate of large complexes and gradual disappearance of smaller complexes until complete electric synchronicity is reached

Digitalis depressed auricular conduction and rate of ectopic discharge when this was low but increased them when the initial rate was rapid It thus converts flutter into fibrillation and tends to perpetuate the latter At the same time electric auricular activity is decreasing

It was concluded that auricular fibrillation is due to an advanced degree of conduction failure which occurs at critical rates of discharge of an ectopic focus It is terminated when conduction from the focus becomes orderly again

Paroxysmal Tachycardia in Infants and Children Study of 41 Cases Alexander S Nadas William Daeschner Arthur Roth and Stanley L Blumenthal[6] (Harvard Med School) found most cases in the first four months of life with the others scattered evenly over the remainder of childhood Most young infants showed no causative factors but over half the older children had diseases that might explain the tachycardia Thirty-one patients were males a predominance observed by others All but one of the patients with idiopathic disease were males the exception was a girl aged 1 day Among the group with known etiology males and females were equally represented Thus the cases divided themselves into two groups one consisting of male infants under 4 months without concomitant disease and the other of older children of either sex who might or might not have a demonstrable cause of the tachycardia Congestive failure developed in a majority of the young infants with paroxysmal tachycardia but in only a minority of the older children Two factors bearing on development of congestive failure were duration of tachycardia at rates over 180/minute and the patient s age A majority of the young age group but only a minority of the older children had failure with paroxysmal tachycardia Electrocardiography

(6) Ped t 9 167 181 F bru ry 1952

showed that 29 patients had supraventricular tachycardia 9 paroxysmal auricular flutter and 3 ventricular tachycardia.

Digitalis nativelle or its equivalent is recommended for termination of supraventricular tachycardia and auricular flutter Optimal digitalizing dose corresponds to 1 0 1 2 mg/sq m body surface or 0 02 0 03 mg/0 5 kg body weight administered in 12 24 hours Ventricular tachycardia responds well to quinidine As a maintenance dose for supraventricular tachycardia and auricular flutter the authors recommend a tenth of the digitalizing dose daily for at least a week possibly longer Quinidine is probably useful in preventing recurrences of ventricular tachycardia and of tachycardias of the Wolff Parkinson White syndrome

Prognosis for life is good Recurrences in the first year are likely beyond that period only the older children and those with the Wolff Parkinson White syndrome have further attacks

Treatment of Urgent Cases of Paroxysmal Auricular Fibrillation Proposed Method for Aiding in Choice between Digitalis and Quinidine Emanuel Hellman M Richard Altcheck and Charles D Enselberg[7] (Gouverneur Hosp New York City) observed 30 paroxysms of auricular fibrillation in 25 patients during two years Nine had heart disease (arteriosclerotic 3 hypertensive 3 rheumatic 1 acute cor pulmonale 2) 13 had toxic or infectious conditions and 3 no demonstrable cause All had rapid ventricular rates Most patients were severely ill and it was felt that the arrhythmia with rapid ventricular rate added to the gravity of the prognosis

Twenty seven paroxysms were treated initially with acetylstrophanthidin (1 2 mg) or ouabain (0 5 mg) intravenously but in only one instance was there reversion to sinus rhythm Also in only one instance did the treatment cause any appreciable slowing of the ventricular rate

Similar results were obtained when 18 paroxysms were treated with digoxin orally (1 5 mg followed by 0 5 mg four hours later) Only once was the rhythm changed and no effects on ventricular rate were noted

Quinidine given orally in 22 paroxysms (five dose courses of 0 2 0 4 Gm every two to four hours increasing by 0 2 Gm

(7) Am J M S 1 655 660 J 1951

during each subsequent course) was successful in all but 2 Reversion usually occurred during the first or second course Total effective dose varied from 0 2 to 7 5 Gm In two in stances conversion of rhythm may have been spontaneous since only single doses had been given Spontaneous remis sions occurred in a number of cases before quinidine could be given and after digitalization had proved ineffective

On the basis of these experiences the authors suggest the following scheme In paroxysmal auricular fibrillation with a rapid ventricular rate a quick acting digitalis prepara tion is given first (Since acetylstrophanthidin is often toxic ouabain strophanthin K lanatoside or digoxin is preferred) If the ventricular rate is slowed digitalization is completed If however the rate is not significantly changed within an hour (depending on the preparation used) quinidine treat ment is immediately begun Digitalis therapy is continued if congestive heart failure is present

Utility and Limitations of Intravenous Quinidine in Ar rhythmias The determination of plasma concentrations of quinidine has led to improved controlled treatment of cardiac arrhythmias Louis J Acierno and Richard Gubner[8] (New York City) have evaluated intravenous administration in doses calculated to give effective plasma levels (4-9 mg /L) much more rapidly than is possible orally They treated 32 consecutive unselected patients with various forms of parox ysmal arrhythmias and 12 selected patients with chronic auric ular flutter fibrillation or extrasystoles Final dosage schedule was 0 06 Gm 0 13 Gm quinidine lactate every five minutes for a total of 0 65 Gm A few patients received additionally 0 3 Gm every half hour or hour for several more doses Continu ous direct writer electrocardiographic control was used

Treatment was successful in half the cases In none of 10 cases was chronic arrhythmia converted to sinus rhythm whereas in 22 of 28 cases of acute arrhythmias (in all but 3 abnormal rhythm had been present less than two days) conversion was achieved There was no definite relation be tween drug effectiveness and type of arrhythmia but patients in congestive heart failure only rarely responded In half the patients the effective dose was 0 26 Gm or less Only four required more than 0 65 Gm for successful conversion

(8) Am H t J 41 733 741 M y 1951

Two thirds of the group and half of the patients in congestive heart failure were digitalized but this had no demonstrable effect on quinidine action

Toxic symptoms in 14 patients were not serious and also were unrelated to dosage Serial ballistocardiographic studies in four patients to evaluate any cardiotoxic effect showed no significant changes

Even in small doses the ECG effects of quinidine appeared when it was given intravenously slowing of circus movement in auricular flutter termination of the arrhythmia and flattening of the T wave with Q T interval prolongation

In four subjects with advanced heart disease fatal arrhythmias developed that were attributable to quinidine In three of these complete heart block and cardiac standstill developed ventricular fibrillation occurred in a fourth Another patient had ventricular tachycardia

Caution and supervision are essential when quinidine is given intravenously It was ineffective and dangerous in patients with congestive heart failure digitalis intoxication and those with bundle branch and heart block There was no evidence that except for its speed of action intravenous injection differed pharmacologically from oral administration

Use of Pronestyl in Treatment of Ectopic Rhythms Treatment of 98 Episodes in 78 Patients Keehn Berry E Lee Garlett Samuel Bellet and William I Gefter[9] (Philadelphia) gave the drug intravenously not faster than 200 mg/minute under constant electrocardiographic control until the ECG showed return to normal sinus rhythm toxic manifestations were observed or 1 Gm had been given Effective oral dose varied widely and was established by trial The usual dose was 0 5 1 Gm every four hours and the maximal dose usually 1 Gm every four hours Indications to stop oral medication were clinical or ECG evidence of toxicity or failure to convert the arrhythmia to a normal sinus rhythm within 24 hours Many patients with conversion to a normal sinus rhythm by either route of administration were maintained for varying periods on oral medication to prevent recurrence Pronestyl converted to normal sinus rhythm 12 of 20 episodes of ventricular tachycardia 30 of 35 episodes of multiple premature ventricular contractions all of 10

(9) Am J M d 11 431-441 O t b 1951

nodal tachycardias (in 2 in which ventricular tachycardia was associated with auricular fibrillation rhythm was re stored to auricular fibrillation) 8 of 12 paroxysmal auricular tachycardias 1 of 8 auricular flutters and none of 7 auricular fibrillations

Although pronestyl is effective when given intravenously oral administration is preferred The most serious toxic mani festation is hypotension which produced coronary insufficiency in two patients and convulsions in two others Frequent blood pressure determinations and a continuous ECG should there fore be obtained during intravenous administration of pronestyl which should be given no faster than 100 mg / minute Mental disturbances were observed in three patients with active toxic processes (rheumatic fever rheumatoid arthritis and hyperthyroidism) Pronestyl given by vein is safer than the corresponding effective intravenous dose of quinidine

Use of Procaine Amide in Cardiac Arrhythmias Herbert J Kayden J Murray Steele Lester C Mark and Bernard B Brodie[1] tested the drug on 54 patients with premature ventricular systoles In some the condition was due to digitalis and in others associated with organic heart disease In all 0 4 1 0 Gm given orally or intravenously abolished the ectopic rhythm Response occurred during or shortly after the injection and within an hour of oral therapy Usual duration after a single dose was three to six hours In 14 patients maintenance doses given every three to six hours prevented recurrence for many weeks In 13 of 15 patients with ven tricular tachycardia normal rhythm was established Ven tricular fibrillation occurred in one before 150 mg had been given The other patient was in extremis all other measures including intravenous administration of quinidine had failed to convert the rhythm Procaine amide was injected intra venously more rapidly than usual and ventricular fibrillation developed When ventricular tachycardia is converted by the drug a supraventricular pacemaker (often the A V node) may be abruptly established or occasional supraventricular beats may interrupt the tachycardia increasing in frequency until the arrhythmia is completely abolished

Auricular arrhythmias were less responsive to procaine

(1) C I t 4 132 J ly 1951

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In four subjects with advanced heart disease fatal rhythmias developed that were attributable to quinidine three of these complete heart block and cardiac stands developed ventricular fibrillation occurred in a fourth A other patient had ventricular tachycardia

Caution and supervision are essential when quinidine given intravenously It was ineffective and dangerous in p tients with congestive heart failure digitalis intoxicat and those with bundle branch and heart block There w no evidence that except for its speed of action intraveno injection differed pharmacologically from oral administrati

Use of Pronestyl in Treatment of Ectopic Rhythm Treatment of 98 Episodes in 78 Patients Keehn Berry Lee Garlett Samuel Bellet and William I Gefter[9] (Phi delphia) gave the drug intravenously not faster than 200 m minute under constant electrocardiographic control until t ECG showed return to normal sinus rhythm toxic manifes tions were observed or 1 Gm had been given Effective o dose varied widely and was established by trial The usu dose was 0 5 1 Gm every four hours and the maximal do usually 1 Gm every four hours Indications to stop o medication were clinical or ECG evidence of toxicity failure to convert the arrhythmia to a normal sinus rhyth within 24 hours Many patients with conversion to a norm sinus rhythm by either route of administration were ma tained for varying periods on oral medication to preve recurrence Pronestyl converted to normal sinus rhythm of 20 episodes of ventricular tachycardia 30 of 35 episod of multiple premature ventricular contractions all of

(9) Am J Med 11 431 441 Oct be 1951

the remaining two died one being in extremis at the time of treatment whereas the other's death may have been due either to the drug or despite it and conceivably might have been averted by a larger dose administered more rapidly

Subjective toxic effects were the exception but objective ones were the rule The latter consisted of fall in peripheral blood and pulmonary arterial pressure increase in circulation time decrease in cardiac output and increase in intraventricular conduction time No serious toxic effects were observed except possibly in one of the two patients with ventricular tachycardia who died

Intravenous administration of procaine amide should be reserved chiefly for patients with paroxysmal rapid heart action who are in immediate danger of death or in whom oral administration of procaine amide or other measures have failed and in patients under anesthesia

Use of Procaine Amide (Pronestyl) in Treatment of Digitalis Induced Ventricular Premature Beats Fr Mainzer[3] (Alexandria Egypt) treated two patients

CASE 1—Man 52 had an old extensive myocardial infarct recurrent femoral phlebothrombosis with several pulmonary embolisms and signs of progressive congestive heart failure Frequent premature ventricular systoles before digitalization increased on 0 20 mg digitoxin daily and increased alarmingly on 0 30 mg daily—necessary for full treatment of the heart failure Other glycosides in corresponding doses caused similar results With progressive heart failure and intolerance to digitalis 2 5 Gm procaine amide (later 2 0 Gm) was given daily with 0 4 mg digitoxin and compensation was complete in two weeks A few premature ventricular systoles were noted only occasionally

CASE 2—Man 51 for several years had congestive heart failure and exertional dyspnea of progressive severity Digitoxin 0 20 0 40 mg daily controlled the heart failure but there were attacks of dyspnea at rest with severe arrhythmias Procaine amide 2 5 Gm (later 2 Gm) daily suppressed the arrhythmia and the same dose of digitoxin was continued

Effectiveness of Procaine Amide in Digitalis Induced Ventricular Tachycardia was studied by L I Goldberg and M deV Cotten[4] (Med College of South Carolina) in dogs under barbiturate anesthesia

METHOD—Digitoxin or ouabain was given intravenously in divided doses until auriculoventricular block with slow ventricular

(3) C d l g 19 93 301 1951
(4) P Soc F p B l & M d 77 741 744 A ɯ t 19 1

amide In none of 10 patients with chronic auricular flutter and 14 with chronic fibrillation given an intravenous injection of 1 Gm over five minutes was normal sinus rhythm re established but there was conspicuous slowing of the f waves The same dose however restored sinus rhythm for several days in two patients with recently established auricular fibril lation One of two patients with nodal tachycardia responded to the dose

Transient ECG changes such as widening of QRS and Q T prolongation were seen in about a third of the patients treated The only toxic symptoms were anorexia nausea and vomiting when large doses were given orally and transient hypotension when the drug was given intravenously

The preferred oral dosage schedule starts with 1 25 Gm followed by 0 75 Gm in an hour if ECG changes are not ob served Further doses of 0 5 1 0 Gm may be given every two hours until there is a response Maintenance doses of 0 5 1 0 Gm every three to six hours have been used Patients with renal insufficiency may have high blood levels The intra venous route is recommended only for critically ill patients or when use of the oral route is impossible Injection rate is 200 mg /minute until the ectopic rhythm has disappeared or 1 0 Gm has been given

Procaine amide apparently is more effective than quinidine in management of ventricular tachycardia or ventricular extrasystoles It may have special prophylactic use in an esthesia and cardiac surgery

Procaine Amide (Pronestyl) in Treatment of Cardiac Arrhythmias J Murray Kinsman Herbert L Clay Walter S Coe and Maurice M Best (Univ of Louisville) treated 41 patients with a total of 51 cardiac arrhythmias and 11 with normal sinus rhythm Dosage was 200 2 000 mg intraven ously In general arrhythmias of supraventricular origin were not affected except for auricular ectopic contractions which were abolished in three of four patients and recent (paroxysmal) auricular fibrillation In two patients with the latter normal sinus rhythm was restored by 300 and 550 mg The transition occurred during the injection Ventricular ectopic contractions were abolished in 12 of 14 patients Ven tricular tachycardia was abruptly stopped in two of four

(2) Tr A Am Phys ans 64 216 2 5 1951

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(4) P o. Soc E p B l & M d 77 741 744 A g t 1951

rate or ventricular tachycardia developed The dose of glycoside necessary ranged from 0 75 to 1 25 cat units/kg given with a two hours Procaine amide in a 10% solution was administered by rapid intravenous injection 10 or 20 mg /kg to animals in ventricular tachycardia and repeated when necessary It was seldom injected until at least 10 minutes of tachycardia with no appearance of normal sinus complexes was recorded Such requirements necessitated relatively high doses of cardiac glycosides and resulted in tachycardia of multifocal origins Criterion for reversion of tachycardia was at least two minutes of ectopic free normal sinus rhythm Thirteen of the dogs were subjected to bilateral cervical vagosympathectomy

There were no differences in the procaine amide action in the vagotomized and nonvagotomized animals Procaine amide was not given six digitalis treated dogs because slow idio ventricular rhythms developed in four and fatal ventricular fibrillation in two

In 8 of 14 experiments ventricular tachycardia reverted to normal sinus rhythm after procaine amide in 5 of these a single injection produced initial reversion The reverted rhythm remained ectopic free in two experiments in the others initial reversion was temporary (average 10 minutes) before reappearance of ventricular tachycardia or appearance of numerous premature ventricular contractions Procaine amide given on appearance of these and subsequent arrhythmias re established normal sinus rhythm No significant ECG changes directly attributable to cumulative procaine amide toxicity were seen Transient bundle branch block however followed injection of procaine amide in four experiments This change commonly reappeared with succeeding administrations in the same experiment Blood pressure usually fell 10 20 mm Hg after doses of 10 mg /kg and 30-40 mm Hg after doses of 20 mg /kg Such hypotensive effects were usually brief and occasionally followed by slight hypertensive effects when tachycardia was reverted In six experiments procaine amide caused slow idioventricular rhythms and cardiac arrest

The effect of procaine amide on the cat unit of ouabain (Hatcher Brody method) was determined in cats End points were obtained electrocardiographically Procaine amide was given by continuous intravenous infusion in five experiments and by rapid intravenous injections in two others The cat unit values determined with ouabain and procaine amide were the same as tho e obtained with ouabain al

Mechanisms of Fluid and Electrolyte Retention in Experimental Preparations in Dogs I Acute and Chronic Pericarditis James O Davis Alan E Lindsay and James L Southworth[5] produced pericarditis by implanting cellophane in the pericardial cavity of trained dogs (in six on the surface of the right atrium and ventricle in seven over the entire cardiac surface) The following studies were then conducted on the unanesthetized animals creatinine and para aminohippurate clearances sodium chloride nitrogen and water balances plasma sodium chloride and protein T 1824 dye space hemoglobin hematocrit body weight arterial and right ventricular pressures and external jugular and femoral venous pressures Potassium clearance and plasma potassium level were determined in five dogs Several control determinations were made about a week apart experimental observations were made at similar intervals Sham operations were performed on two dogs preceded and followed by the prescribed determinations

Two stages of fluid and electrolyte retention were observed After production of pericarditis with fibrous thickening and scarring of the pericardium an acute phase lasted 10 12 days Right ventricular diastolic pressure was increased with equivalent rise in mean right atrial and peripheral venous pressures and decreased peripheral to central venous gradient Edema formed peripherally Simultaneously arterial pressure declined and paradoxical pulse was noted With the end of the acute inflammatory reaction arterial pressure returned to normal and the paradoxical pulse disappeared

During the chronic phase (lasting as long as six months) ascites developed and venous pressure increased it fell immediately after paracentesis Systemic venous right atrial and ventricular diastolic pressures were elevated but arterial pressure was maintained

Sodium chloride and water balances were positive during the acute and chronic phases With this the hemoglobin value and hematocrit reading decreased and the T 1824 dye

(5) B ll J h H pk Hosp 90 64 89 Ja y 1952

space increased When ascites was present potassium bal ance was positive and nitrogen balance negative Glomerular filtration rate and renal plasma flow were increased in acute pericarditis they remained normal or increased in the chronic phase unless protein depletion occurred when the two measurements decreased while the filtration fraction in creased Glomerular filtration rate was not correlated with salt and water retention

The role of venous hypertension in onset of fluid and electrolyte retention during the acute stage could not be de termined because of the possible effects of surgery But in later phases spontaneous diuresis occurred in presence of high venous pressure but did not take place with pronounced decrease in venous pressure

Electrolyte and nitrogen balances were similar in the sham operated dogs and those with acute pericarditis adrenal cortical hyperfunction is suggested as the cause Lower sodium and high potassium fecal concentrations during both phases may have a similar explanation

The authors believe that this study points to altered adrenal cortical function and increased venous pressure as two of the most important factors in pathogenesis of edema and ascites in experimental pericarditis

Congestive Heart Failure Variations in Electrolyte Metab olism with Salt Restriction and Mercurial Diuretics Richard J Stock Gilbert H Mudge and Miriam J Nurnberg[6] (Colum bia Univ) studied seven patients aged 48 70 with heart disease due to hypertension in two arteriosclerosis in three hypertension and arteriosclerosis in one and rheumatic fever in one All were on bed rest and constant low salt diet they were fully digitalized and maintained on constant doses Intramuscular injections of 2 cc mercuhydrin* were given Daily fluid intake (distilled water) was kept constant Balance studies were conducted for periods of a week each Complete balance studies were done on four patients balance figures for Na Cl K and N being obtained from total intake and output Three incomplete balance studies differed only in that each individual food lot was not analyzed and stool electro lytes and nitrogen were not determined A few muscle bi opsies were obtained for electrolyte analyses

(6) C ulat n 4 54 69 J ly 1951

Six of the seven patients lost their edema and became compensated All six showed abnormal electrolyte metabolism in three the heart failure did not respond until electrolytes had been restored to normal The seventh patient in whom severe electrolyte imbalance developed did not respond and died in congestive heart failure Sodium depletion when present was usually symptomless in contrast with adrenal cortical insufficiency

Responses were quite variable When mercurials caused prompt and good diuresis serum electrolyte values were u uallv only slightly abnormal With continued administration hypochloremic alkalosis was observed usually with hyponatremia These changes were not believed due to renal damage since results of the usual clinical renal function tests were normal Metabolic alkalosis may have occurred because patients in congestive heart failure cannot compensate for it by hypoventilation Intracellular potassium deficit was not significant in any muscle studies even when alkalosis was present Furthermore KCl had no significant effect

With continued injections of mercurials there was excessive loss of Cl in the urine which led to hypochloremic alkalosis (with or without hyponatremia) and failure to respond to mercurials When alkalosis was corrected diuretic response recurred The synergistic diuretic effect of ammonium chloride is probably due to its ability to prevent or counteract alkalosis

Cautious administration of hypertonic (5%) NaCl to correct NaCl depletion and improve diuretic response to mercurials gave good results in three cases but its use is not recommended because plasma volume may expand even further and the thirst induced is difficult to control Furthermore diuresis can correct hyponatremia without any change in Na intake

The main conclusions are that mercurial diuretics may severely disturb electrolyte balance and that in turn response of congestive heart failure to their diuretic action depends on a properly balanced electrolyte pattern

Therapeutic Range of Gitalin (Amorphous) Compared with Other Digitalis Preparations According to Robert C Batterman Arthur C DeGraff and O Alan Rose[7] (New York Univ) in most patients on initial slow digitalization a therapeutic range for various digitalis preparations can be demon

(7) C cul t o 5 01 07 F bru y 195

strated by determining the dose required for a therapeutic effect and continuing it until slight toxicity is manifest The percentage of the digitalis preparation needed for a therapeutic effect in terms of the dose required for toxicity represents the therapeutic ratio The smaller the ratio the greater the range With advanced heart disease the dose required for a therapeutic effect may approach the dose which will result in toxicity Because of the small therapeutic range digitalization in such a case is difficult Amorphous gitalin in such circumstances is advantageous since its greater therapeutic range allows digitalization of some patients Moreover toxicity occurring with gitalin will not persist as long as that with the slowly dissipated preparations

With digitoxin average total dose on slow (daily dose of at least two to three times estimated daily maintenance dose) and rapid digitalization were similar and toxic doses for both methods were also the same With gitalin average total dose for both methods was also the same but it was impossible to duplicate the average total dose for toxicity Several patients continued to take a daily dose two to three times the predicted maintenance dose for many days or weeks beyond the anticipated total dose for toxicity This again reflected the *greater therapeutic range for gitalin It was thus possible to* digitalize safely ambulatory patients with mild congestive heart failure

Studies on daily dosage required for maintenance or toxicity revealed that the therapeutic ratio for amorphous gitalin was 41% as compared with 64% for digoxin 65% for digitoxin and 63% for lanatoside C

The therapeutic ranges for gitalin and digitalis leaf as maintenance medication were compared in 18 patients Of these 11 had a greater range with gitalin than with digitalis leaf 6 patients had the same range for both preparations and only 1 had a greater range for digitalis leaf The therapeutic maintenance effect of 0 1 Gm digitalis equaled on the average that of 0 46 mg gitalin toxic effect of 0 1 Gm digitalis leaf was equivalent to 0 65 mg gitalin

In 20 ambulatory patients no longer responding to digitalis and requiring frequent diuretics the smallest daily undivided dose of digitalis leaf causing minimal signs and symptoms of

toxicity was determined by increasing at 8 10 week intervals the daily dosage by increments of 0 05 Gm until toxicity occurred Dosage was then decreased to the maximal tolerated dose Edema continued to accumulate despite this daily maximal tolerated dose Then gitalin corresponding to the minimal toxic dose of digitalis was tried 0 5 mg being substituted for 0 1 Gm digitalis 11 manifested toxicity but 9 tolerated the dose for eight weeks or longer without toxicity and 3 required the next dose level before toxicity occurred Improvement in ambulatory status with decrease in severity of congestive heart failure was noted in 6 of the 20 patients

On the basis of therapeutic range rapid dissipation uniformity from lot to lot constancy in absorption gitalin (amorphous) is the digitalis preparation of choice for treatment of the usual patient with congestive heart failure

Effect of Digitalis Strophanthin and Novurit on Blood Coagulation Venous thrombosis and pulmonary embolism are common complications of congestive heart failure and are believed to be even commoner during treatment This has been explained by the observation that blood coagulation is increased during treatment Soini A N Pere[8] (Helsinki) investigated the mechanism of this effect exerted by drugs used in treatment of congestive heart failure

Of 105 patients in congestive heart failure 37 received digitalis alone 27 strophanthin alone and 41 novurit (a mercurial diuretic) with digitalis or strophanthin Physically healthy subjects with normal cardiovascular and hemopoietic systems were used as controls the corresponding groups containing 41 35 and 37 patients None of the patients had intercurrent disease or had received any time during treatment medication which affects blood coagulation Laboratory and clinical examinations included complete blood count coagulation time calcium time (preferred over blood calcium content) prothrombin index plasma fibrinogen in vitro experiments with the three drugs type and degree of congestive failure (including measurement of venous pressure circulation time daily urine volume and daily weight)

No blood test showed significant change in the treated or control groups except for coagulability In the patients co

(8) A t m d d I 139 pp 251 1950

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completed for 1 3 days After intramuscular injection it is slower although the diuretic effect is almost identical with that of intravenous administration In congestive heart failure excretion takes at least twice the normal time In renal insufficiency it may not be completed for many days even though urinary volume is large

The diuretic action of mercury is principally due to a direct renal effect on the kidney It is believed to be on enzymatic processes concerned with transport and reabsorption of electrolytes in the tubules The precise effect is influenced by existing electrolyte and water balance in the body

Since mercury is a protoplasmic poison toxic effects may result anywhere it contacts tissues in a high enough concentration Thus gastrointestinal symptoms and local irritation may be noted In the doses required for diuresis renal damage is rare even after prolonged administration

Cardiovascular reactions depend on dosage Intravenous injection may cause generalized vasoconstriction and hypertension Cardiac arrhythmias including ventricular fibrillation have been reported Intravenous injections must always be given slowly Fatal reactions have been reported in children when dosage was not properly adjusted to body weight Mercuzanthin® mercuhydrin® and salyrgan® have similar toxicity thiomerin® has fewer cardiotoxic and local irritant effects but is equally potent

Minimal effective dosage should be determined by trial and error Injection of 2 cc daily for congestive heart failure is unnecessary and unwise For maintenance 1 cc given twice weekly is usually sufficient Oral administration is unsatisfactory especially in early treatment of severe congestive heart failure but may be used for maintenance Administration of 0 25-0 33 cc thiomerin® subcutaneously is described as being simple effective and reliable Ammonium chloride often increases the diuretic response to mercurials

In renal insufficiency mercurials must be used cautiously if at all and discontinued if albuminuria hematuria or oliguria develops Failure of response is often due to electrolyte imbalance it should be treated before further injections are given After reactions other preparations or routes may be tried cautiously Since almost all dangerous reactions have

agulation time was shortened after four to six days of therapy averages being 9 8 ± 2 2% with digitalis 11 3 ± 2 7% with strophanthin and 50 4 ± 1 9% three to five hours after novurit injection The only changes in controls were in those receiving novurit who had had reduced coagulation time (average decrease 27 1 ± 1 8%) In all instances of reduced coagulation time this change was associated with diuresis The greater the diuresis the more pronounced the reduction in coagulation time

These studies show that strophanthin and digitalis in patients with congestive heart failure and novurit in normal subjects as well reduce coagulation time by producing diuresis It is thought that this occurs because diuresis (1) increases the blood thromboplastin concentration by way of hemoconcentration and (2) allows tissue fluid (containing thromboplastin) to pass into the circulating blood No specific direct effect of these drugs on blood coagulation was shown which was not related to the degree of their diuretic action

Clinical Aspects of Mercurial Diuretics are discussed by C Thorpe Ray and George E Burch[9] (Tulane Univ) The active principle in all mercurial diuretics is the mercury ion The various compounds differ in toxicity and the rate duration and degree of diuresis they cause Parenteral administration gives the most dependable results intramuscular injection is followed by rapid absorption enhanced by theophylline Absorption is slower from edematous tissues and may result in local reactions Thiomerin® apparently is absorbed satisfactorily from subcutaneous tissue the curve of absorption from muscle is like those for mercuzanthin® and salyrgan ®

Mercury is widely distributed in the body with highest concentrations in kidney and liver It is probably stored in the body combined with tissue proteins With renal insufficiency blood levels may remain elevated and equilibrium of distribution in the body may be reached Small amounts of mercury are also excreted in saliva bile and intestinal mucosa these routes become more significant if there is renal insufficiency After oral administration 50% of the dose is excreted in the urine within 400 minutes After intravenous injection excretion at first is rapid (peak at 20 minutes) but may not be

(9) C cul t 3 9 6 937 J 1951

pacity The fact that the most lasting and surprising recoveries were made by patients with recurrent paroxysmal dyspnea and hemoptysis with concomitant phlebothrombosis like signs in the legs suggests that ligation may also put an end to a source of microemboli not manifest clinically but probably contributory to persisting heart failure

Bizarre Pulmonary Roentgenographic Manifestations in Heart Disease are described by Walter Newman and Harold G Jacobson[2] (Bronx V A Hosp) In one instance encapsulated pleural effusions were at first interpreted as pulmonary metastases Only oblique x ray projections and subsequent changes with treatment confirmed the diagnosis of generalized pleural effusion with interlobar fluid collections A second patient in severe congestive failure had pronounced massive right pleural effusion At that time confined to bed he persistently lay on his right side After 48 hours of lying on his left side also the right hemithoracic density had disappeared from the roentgenogram which now showed generalized pulmonary congestion and cardiac enlargement

In a third case x rays showed nodular and reticulated densities with honeycombing in both upper lobes thought to be inflammatory possibly tuberculous There were also bilateral hilar engorgement and some interlobar effusion After seven days of treatment for congestive heart failure the chest roentgenogram showed no upper lobe infiltrations diminished hilar engorgement and emphysema in both bases The rapid changes in the upper lobes are interpreted as resolution of pulmonary congestion in a patient with emphysema at the bases so that the congestive changes only appeared in the upper lobes

In a fourth patient with congestive heart failure a posteroanterior roentgenogram showed a round nodular density 3 cm in diameter in the right apex which did not respond to penicillin treatment Autopsy three months later proved this shadow to have been due to a rounded 4 cm pulmonary infarct

The authors warn that in congestive heart failure pulmonary congestion effusion or infarction may cause bizarre roentgen shadows mistaken for other conditions

(2) Am Heart J 4 184 193 Aug 1951

followed intravenous injections this route should not be used routinely

Ligation of Vena Cava in Treatment of Heart Failure Pedro Cossio[1] (Buenos Aires) reports on 90 patients aged 27 67 in whom the inferior vena cava was ligated for severe and uncontrollable heart failure Of these 35 had rheumatic valvular defect 48 hypertension with or without coronary arteriosclerosis 5 syphilitic aortic regurgitation and 2 interauricular septal defects Of the first 20 5 died 12 hours to 7 days after surgery 4 of peripheral circulatory failure and 1 of abrupt accentuation of the heart failure Of the other 70 only 4 died in the same period 2 in collapse and anuria 1 with collapse alone and 1 of rapid aggravation of the heart failure All but 1 of the other 81 patients tolerated surgery without particular distress

Early results showed no appreciable improvement in 18 and appreciable sometimes even spectacular improvement in 63 Appreciable improvement means eradication of orthopnea and diminished pulmonary and liver congestion edema and ascites if previously present It generally coincided with reduction of heart size (sometimes impressive) disappearance of gallop rhythm and pulsus alternans fall of venous pressure in the arms with no increase when legs were raised reduced elbow lung and elbow tongue circulation times increased vital capacity and decreased blood pressure in the right heart

Improvement persisted for months in 51 and for two years the maximum observation period in 40% of those who showed early improvement Improvement was sustained if patients continued medical treatment for heart failure although most did not adhere as strictly as before surgery With unchanged or nearly unchanged administration of digitalis and sodium restriction the patient s dry weight could be maintained even when mercurial diuretics were spaced out and he was allowed greater activity Whenever patients neglected these precautions heart failure returned but it could again be controlled by resuming medical treatment

At first early improvement was attributed to reduction of venous return with consequent improvement of cardiac ca

(1) Am He t J 43 97 10 J y 1952

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PULMONARY CIRCULATION

Cor Pulmonale in Infancy and Early Childhood Report on 34 Patients, with Special Reference to Occurrence of Pulmonary Heart Disease in Cystic Fibrosis of Pancreas Cor pulmonale is thought to be secondary to obstructive lung disease but Stephen W Royce[3] (Babies Hosp New York City) reports on 34 patients all but 2 under age 6 There were 28 with fibrocystic disease 15 had had congestive heart failure

Anatomic criteria of cor pulmonale were (1) right ventricular hypertrophy (2) right auricular hypertrophy and dilatation (3) usually pulmonary artery and conus dilatation with lumen thickening and (5) significant lung disease By these criteria correlated with clinical data 25 patients had chronic and 3 subacute cor pulmonale with fibrocystic disease 2 had acute cor pulmonale due to obstruction of pulmonary circulation by foreign bodies and 1 each had cor pulmonale due to bronchiectasis tuberculosis interstitial pneumonia and diaphragmatic hernia

Emphysematous changes were pronounced in all The heart though seldom enlarged showed increased weight and gross and microscopic evidence of right ventricle hypertrophy

Among the patients with fibrocystic disease the degree of pulmonary involvement determined the severity of the condition and life expectancy The earlier in life cough first appeared the more serious the prognosis If it appeared in babies life was usually very short Thus half of the deaths occurred in infancy and all but 15% of patients died before reaching age 5

Use of antibiotics tends to increase incidence of chronic cor pulmonale prolonging the course and changing the type of death from a respiratory to a cardiac one Clinically when lung disease of whatever type was severe enough to cause cor pulmonale respiratory symptoms masked the cardiac ones Treatment of the secondary heart disease was unavailing since the causative lung disease was usually incurable In a few instances epinephrine like compounds produced dramatic but temporary improvement

(3) Ped [illegible] 8 233 274 August 19[illegible]

Clinical diagnosis of cor pulmonale was often impossible Fluoroscopic signs of right ventricular enlargement were often lacking circulation was normal and venous pressure was only rarely elevated and then only when congestive heart failure was obvious Polycythemia was not consistently present and showed no correlation with degree of emphysema and cor pulmonale Electrocardiographic changes were rarely specific

The pathogenesis of cor pulmonale in these children has two possible mechanisms either pulmonary hypertension increases sharply in a few minutes or hours putting a strain on the heart for which it cannot compensate (e g foreign body in the pulmonary circulation rapid progression of fibrocystic disease) or the lung disease gradually progresses with pulmonary hypertension for which the heart can compensate by hypertrophy although ultimately congestive heart failure results

Primary Pulmonary Hypertension I Clinical and Hemodynamic Study of three patients is presented by David T Dresdale Martin Schultz and Robert J Michtom[4] (Brooklyn) Salient clinical features are exertional weakness and dyspnea in patients who later have right heart failure without antecedent cardiac or pulmonary disease Effort syncope and angina are most significant when present Sudden death is not uncommon Physical examination shows normal systemic blood pressure clear lungs accentuated pulmonic second sound and variability or absence of heart murmurs Venous distention and hepatomegaly occur unassociated with peripheral edema or ascites except late in the course Cyanosis when present is a terminal feature unless the disease is complicated by patent foramen ovale This syndrome has been seen in both sexes at all ages but is commonest in the 20–40 year age group

The ECG s are consistent with right ventricular hypertrophy Typical x ray signs are right ventricular enlargement bulging pulmonary artery segment prominent hilar vessels and normal or diminished intrapulmonary vascular markings Pronounced right ventricular hypertrophy is constant but the pulmonary vascular changes proximal to the capillary bed vary considerably In some cases no significant pulmonary vascular changes are noted

(4) Am J Med 11 686-705 D mb 1951

Pulmonary function studies in two patients ruled out intrinsic lung disease in both Right heart catheterization in all three showed elevated pulmonary artery right ventricular end diastolic pressures diminished cardiac output increased arteriovenous oxygen difference and normal arterial blood oxygen saturation *Blood volumes and hematocrit* readings were *normal in two and slightly elevated in one* One had no clinical evidence of right heart failure and none had edema A seven to ninefold increase in pulmonary resistance was calculated at rest Physiologic and autopsy studies supported the *view that the locus of increased resistance was in the small pulmonary arteries Isolated overactivity of the sympathetic* nervous system was suggested by the pronounced effect of priscoline® in lowering pulmonary artery blood pressure

Radiologic Study of Pulmonary Infarction D S Short[5] studied 120 patients with pulmonary thromboembolism of whom 94 had radiologic examinations Almost half the patients had heart disease one quarter had recently been operated on and one sixth were obstetric patients

X ray *diagnosis of infarction* was made in 85 In 75 the infarct itself could be seen 48 had evidence of pleural involvement 28 with effusion and 31 had elevation of the diaphragm Thus one of the diagnostic triad—elevation of the diaphragm an infarct shadow pleurisy—was present in each Half the infarcts occurred in the right lower lobe another *third in the* left lower lobe Multiple pulmonary infarcts were visualized *in almost half the cases*

The infarct shadow was only rarely triangular *most frequently* it consisted of an area of consolidation Occasionally streaking at one base was the x ray clue Whatever the specific pattern it took at least 12 hours for changes to be apparent in the roentgenogram Resolution was normally rapid and almost complete within two to four weeks except in the presence of severe pulmonary congestion During resolution transient linear shadows were often seen probably representing local atelectasis

Negative x ray results may be due to the infarct shadow being hidden behind the diaphragm or heart pulmonary congestion hydrothorax embolism without infarction time of examination or inadequate technic In such a case when roent

(5) Quart J Med 20 33 45 July 1951

gen confirmation of the clinical diagnosis is important re examination and use of lateral views fluoroscopy and tomography may be helpful Differentiation from collapse subphrenic abscess lobar pneumonia and pleural effusion may be difficult A costophrenic infarct may be mistaken for fluid except that its upper shadow is usually irregular and convex upward

Chest Pain in Association with Pulmonary Hypertension Its Similarity to Pain of Coronary Disease is discussed by William N Viar and T R Harrison[6] (Med College of Alabama) Location radiation quality and intensity of the pains seem identical Additional features enhance the difficulty of differentiation Thus some patients with pulmonary hypertension complain of pain on exertion relieved in a few minutes by rest Others have prolonged bouts of pain associated with electrocardiographic changes The most important clue comes from recognition of a condition capable of causing pulmonary hypertension Commonest underlying disorders are lesions of the mitral valve usually stenotic but occasionally regurgitant primary diffuse disorders of the lungs especially asthma emphysema and bronchiectasis disorders of the pulmonary arteries of which embolism is the most common and congenital heart malformations which lead to elevation of pulmonary artery pressure Not all patients with these disorders complain of pain it is absent in most instances It is rarely if ever encountered in patients with pulmonary hypertension secondary to left ventricular failure

Aside from clinical and x ray evidence of an underlying disease capable of elevating pulmonary pressure the following clues not invariably present may be helpful history of long standing cough cyanosis persistent or intermittent and usually present during the episodes of pain association of pain and dyspnea pain on breathing (unusual in patients with angina pectoris but not rare with myocardial infarction particularly when associated with pericarditis) variability of duration of pain Clinical evidence of right ventricular hypertrophy is one of the most valuable differential points In the absence of disorders like thyrotoxicosis anemia and severe anxiety states which lead to increase in cardiac output diffuse forceful pulsations over the whole left precordium give strong

(6) C cul tio 5 1 11 J u ry 1952

evidence for right ventricular enlargement In patients with thin chest walls and without dyspnea this simple clinical phenomenon is likely to be more reliable than ECG or x ray evidence

The ECG changes may or may not be present in patients with pulmonary hypertensive pain Their absence is evidence against myocardial infarction Signs of tissue destruction (fever leukocytosis rapid sedimentation rate) occur in patients with pulmonary hypertensive pain only when there is infarction or lung infection Striking relief of pain with oxygen inhalation speaks for pulmonary hypertensive pain there may be slight or no relief either with this type of pain or that due to coronary disease Nitroglycerin either has no effect or only a minimal palliative effect on pulmonary hypertensive pain This does not aid in differentiation from myocardial infarction but is important in excluding effort angina or status anginosus

Effort Syncope as Early Manifestation of Primary Pulmonary Hypertension Three cases reported by William Dressler[7] (Maimonides Hosp Brooklyn) and six from the literature had in common syncope on effort dilatation of the pulmonary artery and evidence of right ventricular hypertrophy and absence of common causes of right ventricular hypertrophy especially of rheumatic valvular lesions congenital heart disease and chronic pulmonary disease These features suggest primary pulmonary hypertension In three patients cardiac catheterization revealed pronounced pulmonary hypertension Autopsy in seven cases revealed pulmonary arteriosclerosis in at least two being too mild to explain right ventricular hypertrophy In one case cardiac catheterization revealed severe hypertension in the lesser circulation and autopsy failed to show enough pulmonary arteriosclerosis to account for right ventricular hypertrophy

The syncope suggested that of angina pectoris notably with regard to the precipitating factors e g running for a bus pushing a baby carriage uphill climbing upstairs and excitement It was often preceded by premonitory symptoms light headedness dizziness feeling of epigastric fulness choking or tightening around the heart Unconsciousness lasted a few seconds to 25 minutes During attacks cyanosis and ma

(7) Am J M S 223 131 143 February 1952

cular rigidity were often present Some patients were incontinent No tongue bite was reported Nausea vomiting abdominal cramps and diarrhea often followed attacks After seizures of syncope the patient felt weak and nervous for some days The *number of attacks varied from two to innumerable* The causal relation between attacks and pulmonary vascular disease was recognized in only a few cases

Effort syncope seems to be characteristic of primary pulmonary hypertension It does not occur in pulmonary hypertension secondary to chronic pulmonary disease valvular lesions or congenital heart disease Loss of consciousness may occur in chronic pulmonary disease during severe coughing but not with other efforts or with excitement

Effort syncope not an invariable feature of primary pulmonary hypertension is a useful diagnostic sign when present it may allow early diagnosis before congestive failure or even manifestations of right ventricular hypertrophy have appeared Combined with evidence of right ventricular hypertrophy or dilatation of the pulmonary artery or both it is highly suggestive of primary pulmonary hypertension Severe cyanosis usually cited as an important and even indispensable sign of obstructive pulmonary arteriosclerosis is neither a constant nor an invariable feature its diagnostic value has been greatly over rated

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CEREBRAL VASCULAR DISORDERS

Factors Influencing Cerebral Blood Flow and Metabolism A Review is presented by Peritz Scheinberg and Harold W Jayne[8] (V A Hosp Coral Cables Fla) Development of the nitrous oxide technic for calculating cerebral blood flow has enhanced accurate study of the varied factors Normal cerebral blood flow (65 ml /minute/100 Gm brain) is about 14% of total cardiac output The brain consumes 22% of total body oxygen and about 70% of total glucose output of the normal liver

Although apprehension artificial fever and hyperthyroidism increase total body metabolism cerebral blood flow remains normal In essential hypertension vascular tone

(8) C l t 5 2 5 236 F bru y 195

throughout the body including the brain increases as does cerebral vascular resistance but blood flow remains constant. Uni or bilateral stellate procaine block does not change cerebral flow metabolism or vascular resistance of normal adults of patients with essential hypertension or cerebral vascular disease or of most patients with acute cerebral vascular accidents Bilateral stellate ganglionectomy may reduce cerebral vascular resistance in parkinsonism Nicotinic acid even in large intravenous doses does not change cerebral blood flow nor does procaine or histamine intravenously Flow is also normal in schizophrenics Insulin hypoglycemia and uremia reduce cerebral metabolism but do not alter flow Desoxycorticosterone glucoside does not change cerebral blood flow or oxygen consumption but it greatly decreases arteriovenous glucose difference and cerebral glucose consumption Toxemia of pregnancy or tilting the patient s head up 20 degrees causes no change

Cerebral blood flow is increased by 5 7% CO_2 diabetic coma anoxia (10% O_2) and anemia of acute blood loss Increased flow with cerebral hemangioma results from arteriovenous shunts Slightly increased flow with thiopental anesthesia may be due to increased CO_2 in such anesthesia A similar slight increase during natural sleep is unexplained Papaverine apparently directly dilates cerebral vessels increasing cerebral blood flow

Cerebral blood flow may decrease with normal decreased or increased cerebral oxygen consumption and even with decreased cerebral vascular resistance It is reduced in hyperventilation inhalation of 85 100% oxygen polycythemia motionless standing increased intracranial pressure cerebral vascular disease heart failure with administration of aminophylline or caffeine in myxedema pernicious anemia diabetic acidosis pentothal* narcosis and on administration of ACTH or cortisone Flow is also decreased in dementia paralytica and meningovascular syphilis probably because of small vessel occlusion Generally reduced cerebral metabolism can induce increase in cerebral vascular resistance and decrease in blood flow

Use of Dramamine* in Vestibular Disturbances Complicating Hypertensive and Arteriosclerotic Disease was investi

gated by I Ralph Goldman Neuton S Stern and Thomas N Stern[9] (Univ of Tennessee) Vestibular disturbances common in cardiovascular conditions are due partly at least to vascular changes Symptoms consist of vertigo on sudden head movement less severe the slower the motion and disappear when the patient lies still Because of its effect in motion sickness dramamine® was given 15 patients with some form of cardiovascular disease and symptoms of vestibular dysfunction Most of them had tried other drugs without success Each received 25 100 mg dramamine® four times daily and was frequently interviewed about effects of the drug Ten patients were completely relieved three conspicuously improved and two had no change There were no unpleasant side reactions

Use of Nicotinic Acid in Cerebrovascular Disturbances Especially after Apoplexy with Hemiplegia J Mentha and J Stepanovicius[1] (Berne) treated 20 patients whose condition had remained stationary after apoplexy due to cerebral hemorrhage embolism or a focus of softening with hemiplegia or pronounced hemiparesis Nicotinic acid was given intravenously (up to 50 mg daily) or orally (up to 300 mg daily) Close observation of 13 before treatment permitted accurate evaluation of the direct effects 10 had notable increased motility and 3 were not improved The other seven responded but improvement could not be attributed with certainty to the drug Therapy did not prevent recurrence of apoplectic seizures In 10 patients with disturbed cerebral blood circulation but no seizures but with predominant complaints of headache or giddiness similar treatment definitely lessened but did not abolish symptoms in 7 Nicotinic acid had no untoward effects and in the long run did not affect blood pressure

Communications between Carotid Artery and Cavernous Sinus Clinical and Critical Study of Their Complications and Treatment is presented by Emile Holman Frank Gerbode and Victor Richards[2] (Stanford Univ) In 12 patients with communications between the carotid artery and cavernous sinus 34 operations were required to control the bruit Early control of the fistula by multiple operations if necessary is

(9) Am H t J 42 30 307 A gu t 1951
(1) H l t m d cta 6 608 631 Dec mbe 1951
(2) A g l gy 2 311 339 Octob 1951

throughout the body including the brain increases as does cerebral vascular resistance but blood flow remains constant. Uni or bilateral stellate procaine block does not change cerebral flow metabolism or vascular resistance of normal adults of patients with essential hypertension or cerebral vascular disease or of most patients with acute cerebral vascular accidents Bilateral stellate ganglionectomy may reduce cerebral vascular resistance in parkinsonism Nicotinic acid even in large intravenous doses does not change cerebral blood flow nor does procaine or histamine intravenously Flow is also normal in schizophrenics Insulin hypoglycemia and uremia reduce cerebral metabolism but do not alter flow Desoxycorticosterone glucoside does not change cerebral blood flow or oxygen consumption but it greatly decreases arteriovenous glucose difference and cerebral glucose consumption Toxemia of pregnancy or tilting the patient s head up 20 degrees causes no change

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Use of Dramamine* in Vestibular Disturbances Complicating Hypertensive and Arteriosclerotic Disease was investi

one died In one case when unilateral ligation and division of the carotids had not controlled the bruit cure followed division of small arteries palpable in the supraorbital and infraorbital areas Normal vision in the affected eye followed control of bruit in only 3 of 12 patients Ocular complications limited to the affected eye were extraocular muscle palsies in 6 exophthalmos in 11 cataracts in 3 glaucoma in 4 enucleation in 1 and impaired vision in 9

Intracranial Venous Thrombosis as a complication of general diseases is reviewed by H C Koek (Heerenveen The Netherlands) and J Th R Schreuder[3] (Sneek) Three cases are reported in two of which the condition followed labor Intracranial venous thrombosis is not a rare complication of the puerperium The disease usually begins 4 21 days after delivery Pregnancy confinement and puerperium were usually normal until the acute symptoms appeared The main symptom is abrupt onset of convulsions usually focal then spreading rather quickly Prolonged attacks are usually followed by coma After the convulsions paralysis may appear limited to one side of the face or spreading to one side of the body sometimes complicated with aphasia In extensive thrombosis cranial venous congestion may increase intracranial pressure with headaches vomiting and even papilledema Cerebrospinal fluid may be normal in the first stage later pressure may be increased and with hemorrhage the protein content may be increased and erythrocytes found Thrombosis in other veins especially of the legs may be present All three patients had convulsions focal in one generalized in two

Intracranial venous thrombosis has been misdiagnosed as cerebral embolism from venous thrombosis in the legs presuming presence of a patent foramen ovale Patent foramen ovale in an anatomic sense is found in 25 30% of autopsies in a functional sense in only 1% In the former an embolus may be pressed through a narrow foramen ovale usually only if pressure in the heart has increased by repeated pulmonary emboli m Convulsions after delivery are often diagnosed as late eclampsia If high blood pressure or albuminuria was not present during pregnancy intracranial venous thrombosis is a more probable diagnosis particularly if the disturbance be

(3) A t p ych t et eu l 6 353 357 1951

mandatory to avoid disabling symptoms Digital compression of the common carotid on the side of the lesion should be done many times daily for several weeks before operation to insure adequate collateral circulation when the carotid is ligated Ligations should be done under local anesthesia Temporary occlusions are maintained for about one hour before permanent occlusion is effected to determine if symptom of cerebral ischemia will appear If they do the occlusion is removed and operation is delayed for two weeks while repeated digital compression of the artery is continued In two instances of ligation in continuity of the common carotid and in two such ligations of the internal carotid the lumen was re established at the site of ligation requiring secondary ligations The occurrence in two cases of delayed hemiplegia after 24 and 48 hours suggests that the first operation should consist of occlusion of the common carotid with a broad fascial band which may be removed if necessary to be followed by ligation and division of the external and internal carotids should the bruit persist or recur

In the presence of a carotid cavernous fistula occlusion of the common carotid may be followed by reversal of flow from the external into the internal carotid In three patients in whom this reversal of flow takes place ligation of the internal carotid at a second operation controlled the bruit This suggests that delayed hemiplegia may be prevented by graded occlusion of the carotids occlusion of the common carotid by a fascial band at the first operation and if bruit persists or recurs ligation and division of the external carotid several weeks later Concomitant ligation of the internal jugular vein at the time of common carotid occlusion is necessary to obstruct the easy return flow of blood through the fistula back to the heart but it should be performed cephalad to the entrance of the external facial vein to avoid congestion of the orbit and its contents In 10 patients in whom concomitant ligation of the internal jugular was performed 20 operations were necessary in 2 others only one operation in each was necessary

Intracranial occlusion of the internal carotid may be necessary to control the fistula when occlusions in the neck have failed Intracranial clipping of the internal carotid was performed in five patients with satisfactory results in four

hydroergocornine are seldom beneficial in prolonged treatment and have dangerous side effects Anticoagulants have not been used by de Takats Indications for lumbar or dorsal sympathectomy are postembolic or thrombotic ischemia of the extremities endarteritis and arteriosclerosis obliterans and such neurovascular states as causalgia and Raynaud s syndrome Amputation may be necessary Minor amputations done in time may prevent more formidable ones later Histamine injections are useful *in determining the level of amputation*

In neurovascular lesions of the extremities osteoarthritis of the spine scalenus syndrome and herniated disks must be considered in differential diagnosis Diabetic neuropathy may respond to injections of vitamin B_{12} 15 μg twice a week followed by maintenance dose of 25 μg orally if there is satisfactory response

Erythermalgia a symptom rather than a disease requires treatment of the underlying condition Sympathectomy may relieve the burning pain but sympathetic procaine block should always be done first

Postphlebitic and Varicose Venous Stasis Clinical Results of Treatment by Pulsatile Air Pressure Principle W J Merle Scott[5] (Univ of Rochester) points out that varicose veins are always associated with valve destruction or incompetence However there are two types of such valvular dysfunction (1) valves of the saphenous systems are incompetent but those of the perforators are not (2) perforator valves are incompetent allowing the superficial veins to fill from the deep ones In type 1 ligation of the main superficial venous trunk above all branches usually is successful but in type 2 venous stasis is not permanently benefited

In chronic postphlebitic lymphedema perforator valves are inflamed disturbing function as do type 2 varicose veins except that there may also be partial obstruction to lymph return

Because all methods of treating venous stasis due to incompetent perforators have serious defects a legging of inelastic material containing an inflatable rubber bladder whose pressure can be regulated was constructed Leg muscle contraction causes rhythmic rise in air pressure to the skin (pulsating air pressure) aiding venous return from the super

(5) J A M A 147 1195 1 01 No 24 1951

gins after the 4th postpartum day Intracranial venous thrombosis in the puerperium suggests thrombosis in the pelvic veins in one case intracranial thrombosis with uterine carcinoma suggested the same relation

Anticonvulsants should be given for at least a year afterward Caution in use of anticoagulants is recommended

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PERIPHERAL VASCULAR DISORDERS

Diagnosis and Management of Peripheral Vascular Disease According to Geza de Takats[4] (Univ of Illinois) a few simple clinical tests usually suffice to evaluate peripheral vascular status Thus the nature of the pulse color changes venous filling time reactive hyperemia and oscillometric readings usually give most of the desired information A skin thermometer can be used to register changes before and after nerve block An angiogram may occasionally direct treatment An ECG nonprotein nitrogen blood sugar and blood cholesterol determinations and overnight urine concentration test provide valuable information

Acute arterial occlusion requires immediate treatment Papaverine (0 03 Gm) and heparin (10 cc of a 1% solution) intravenously or better still intra arterially are tried first but are never given in the same syringe If there is no response the regional sympathetics should be blocked As last resort embolectomy should be done within 6-12 hours after onset if the lower extremities are involved Recurrent emboli may require prolonged use of dicumarol* although this has not been too successful Acute arterial thrombosis requires the same treatment except for embolectomy

Aneurysm usually is treated surgically Wiring and/or wrapping of syphilitic and arteriosclerotic aneurysms and those due to cystic medial necrosis is advised

In chronic arterial occlusions physical therapy especially intermittent venous hyperemia is often beneficial results being conditioned by duration and severity of the disease Roniacol* (an alcohol of nicotinic acid) 50 100 mg doses three or four times daily increases pulse volume Priscoline* tetraethylammonium chloride dibenamine* histamine and di

(4) M Cl N th Am ca 36 141 158 J y 195

without ulceration were completely relieved Of five with intractable pain with ulceration one was relieved completely and the others to varying extent

Eight patients with itching (four with pruritus vulvae) were relieved in three to seven days One with pruritus ani did not respond One with osteoporosis and pain in hands and feet had unexpected pain relief after other prolonged therapy had failed Two patients had completely resistant ulcers of the inner ankle where osteomyelitis had left the skin directly adjacent to bone With my b den healing was promptly accelerated and complete in three weeks

Intra arterial Histamine in Treatment of Occlusive Peripheral Arterial Disease John A Dixon W J Merle Scott and Marvin A Epstein (Univ of Rochester) treated eight men with refractory intermittent claudication

Before injections in a constant temperature room the skin temperature response in the lower extremities to immersing the arms in hot water was measured If the temperature in the affected leg did not rise significantly a posterior tibial nerve block was performed with 1% procaine and the temperatures again measured On several patients a paravertebral block or spinal anesthetic was given as a further check All eight patients showed little temperature response ischemia was due to arterial occlusion rather than spasm Three mg histamine diphosphate in 500 cc normal saline was given into the femoral artery in a half hour The usual schedule was two injections weekly for three weeks then one injection weekly until walking tolerance was stabilized Injections were then discontinued and walking tolerance checked at monthly intervals With regression weekly injections were reinstituted All patients were followed a minimum of five months Walking tolerance was estimated with a treadmill The pain end point was distinct in most patients

After injection thigh skin temperature increased early but that of the toes increased little or even decreased initially Early several patients had seeming further impairment of circulation in the foot but this was always transitory followed immediately by typical erythema and increase in skin temperature With temperature elevation skin color on the toes changed to a much brighter pink on standing

(7) C cul t 5 661 669 M y 19

ficial veins This legging has prevented or reduced post phlebitic or varicose stasis except during acute inflammation Subcutaneous induration gradually improves in 6-12 months Of 105 postphlebitic and varicose ulcers 89 healed while the patient was ambulatory Often other treatment had failed

To avoid failures or complications mechanical faults and incorrect fitting or inflation of the legging must be prevented Topical treatment can be used with the apparatus and dressings and bandages should be changed often enough especially during the first few days to avoid excess moisture Fungous infections usually heal with zincundecate powder

Muscle Adenylic Acid Clinical Study of Its Effect Elias D Lawrence David Doktor and Jack Sall[6] (Paterson N J) gave my b den sublingually or intramuscularly to 23 patients with varicose veins and their complications 9 with obliterative arteriosclerotic peripheral vascular disease and 13 with various pruritic and ulcerative disorders Sublingually an adequate fairly uniform effect was obtained from a 20 mg tablet every hour five times a day until symptoms were relieved this varied from three days to three weeks A 40 mg maintenance dose was then given if needed No untoward symptoms or reactions developed Intramuscularly sustained action my b den was given as one 20 mg injection daily for 3 days then one injection every 48 hours The injections were painless and there were no reactons

Of the 23 patients with vein lesions 2 had low grade superficial thrombophlebitis without demonstrable varicose veins 16 superficial thrombophlebitis with varicose veins and 5 chronic deep thrombophlebitis with stasis edema itching burning pain and scaling of skin with oozing ulcerations All but two responded well Itching and burning were re lieved and usually gone in two to four days There was con tinuous gradual transformation of scaling oozing eczematous rough skin to smooth soft wrinkly skin varying from com plete to partial response Induration swelling pain and tender ness decreased despite ambulatory treatment without elastic support

My b den was given nine patients with advanced oblitera tive arteriosclerosis unrelieved by sympathectomy nerve block vasodilators and narcotics Two with intractable pain

(6) A x l gr 2 405 411 Oct be 1951

injections of hexamethonium (C6) to 16 hospitalized patients with thrombophlebitis of the lower extremities Dramatic and almost immediate relief from pain and tenderness was seen in each One patient required seven days to become asymptomatic the others walked without discomfort by the fifth day In 14 other patients (5 with obliterative arteriosclerosis 3 Buerger s disease 2 Raynaud s phenomenon 2 arterial embolism 1 primary arterial thrombosis and 1 causalgia) injection of C6 was as effective as paravertebral block Its advantage is that it can be given by nurses at regular intervals to maintain increase in peripheral blood flow the disadvantage is hypotension especially in the erect position

In elderly hypertensive or debilitated patients it is best to give 1 mg/minute intravenously while blood pressure is determined repeatedly After 10 mg has been given the injection rate can be increased If pronounced hypotension occurs injection is halted the foot of the bed elevated the lower extremities are raised and neo synephrine® is injected intravenously Epinephrine should not be u ed Because of postural hypotension the patient should remain supine for two to three hours after each injection With subsequent injections there may be constipation and occasionally ileus both readily controlled by urecholine® or other parasympathetic agent enemas and cathartics

The usual dose of C6 was 50 mg intravenously or intramuscularly An oral dose of 830 mg (1 5 Gm of the dibromide salt) had about the same effect as the smaller parenteral dose All patients who responded well also had good results after sympathectomy the converse however does not follow

Effect of Local Application of Glyceryl Trinitrate (Nitroglycerin) on Raynaud s Disease and Raynaud's Phenomenon Studies on Blood Flow and Clinical Manifestations are reported by Martin S Kleckner Jr Edgar V Allen and Khalil G Wakim[1] (Mayo Clinic and Found) Blood flow in the extremities (whole forearm and leg) was measured by a plethysmograph and the temperature of fingers and toes by a galvanometer Tests were made at constant temperature with the subject at rest Control values were taken the test ointment (2% glyceryl trinitrate in a lanolin base) was applied removed 20 minutes later and flow and temperature readings

(1) C irc l t n 3 681 689 May 1951

All patients but one had a definite increase in walking tolerance Of the seven given a course of histamine injections five had good results one fair and one poor Relation of increase in exercise tolerance to the patients demands was considered in evaluating results Thus a small increase in a cardiac patient may be a good result Apparently patients who will be appreciably helped by histamine injections show definite evidence of increased walking tolerance by about the sixth injection Good erythema below the knee during the first injection was a good prognostic sign

Intra arterial Treatment of Obliterative Peripheral Vascular Diseases with Tetraethylammonium Bromide Otto Selvaag and Rolf Holmboe[8] treated nine patients with arteriosclerosis obliterans three with diabetes plus arteriosclerosis and three with late results of arterial embolism A 10% solution was injected into the femoral artery 2 4 ml was injected in two to four minutes two or three times weekly for two weeks followed by injections at intervals of one to three weeks to a total of 8 10 or 12 injections No severe reactions were seen although occasionally slight symptoms of hypotension followed injection

Results were judged chiefly by subjective improvement of symptoms causing most discomfort susceptibility to cold and intermittent claudication Decrease of coldness of feet was noted by all patients with postembolic insufficiency or arteriosclerosis without diabetes Good results were noted even in long standing cases (13 and 18 years) the patients could get about even in midwinter walking pains were lessened and the feet were warmer Two with diabetes were little improved No patient was worse and none wholly unrelieved In addition to diminution of claudication there was greater ease in the involved limb

The brief observation (three to five months) does not permit conclusions but further trial seems warranted Only one patient with satisfactory response relapsed in three months a second course gave relief

Clinical Appraisal of Hexamethonium (C6) in Peripheral Vascular Diseases Frank A Finnerty Jr and Edward D Freis[9] (Georgetown Univ) gave intravenous or intramuscular

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(8) Acta med sc d av 14 132 142 195
(9) N w E gl d J Med 245 3 5 3 8 A g 30 1951

the superficial femoral artery and vein in the midpoint of the adductor canal with proximal ligation of the vein the diameter of the stoma was made to equal that of the artery Follow up varied from 4 to 10 months In nine instances there was permanent warming of the extremity but not down *to the foot Seven patients had postoperative edema of the* leg and foot that disappeared after a few weeks in all but one Six patients required amputation despite the shunt (four below and two above the knee) There was little bleeding from either artery or vein in five of these

This procedure may be valuable if the following problems can be solved (1) Should distal venous tributaries be ligated? (2) Is there sufficient capillary oxygen exchange? (3) Do the venous valves offer much resistance to arterial flow? (4) Do the anastomoses remain patent? (5) Will there ultimately be cardiac damage?

Early Clinical Sign of Venous Thrombosis is described by Arthur J D Alessandro[3] (Presbyterian Hosp Newark N J) Decided diminution or even absence of the femoral pulse in the affected extremity particularly on palpation of the pulse preparatory to vein ligation is invariably present despite absence of other appreciable signs or symptoms In six months two cases of serious but nonfatal pulmonary emboli were observed in which this unilateral change in the femoral pulse was the only significant clue to the affected extremity Severe and early angiospasm attends all vascular accidents to any extremity regardless of location of the thrombus This angiospasm is readily appreciated by anyone who has successfully performed lumbar sympathetic block on a patient with venous thrombosis

The change in femoral pulse occurs early in both thrombophlebitis and phlebothrombosis long before edema or swelling is demonstrable Observation of the femoral pulse should be part of the daily postoperative routine

Effect of Drugs Used in Treatment of Intermittent Claudication on Exercise Tolerance of Individuals with Obliterating Arteriosclerosis In patients with intermittent claudication exercise tolerance (two step test) remains constant when repeated on the same day The acute effects of various drugs on in

(3) J A M A 147 1759 1 60 D 9 1951

were taken at 30 45 and 60 minutes after application The other limb was used as control by simultaneously applying lanolin base Tests were made on three patients with Raynaud s disease and six with Raynaud s phenomenon due to acrosclerosis (two patients) and thromboangitis obliterans arteriosclerosis obliterans livedo reticularis and occupational occlusive arterial disease (one each) In a parallel series (11 patients with Raynaud s disease and 2 with Raynaud s phenomenon—1 with arterial occlusive disease and 1 with acrosclerosis) similar measurements were made but a special hand plethysmograph was used to study digital blood flow changes separately

There was a significant increase in blood flow and skin temperature of the digits of the 14 patients with Raynaud s disease Control extremities showed a smaller and delayed increase due to absorption of glyceryl trinitrate simultaneous nitrite headaches were common Increases in blood flow and skin temperature with Raynaud s phenomenon were much more variable Ointments of 10% priscoline[®] 5% nicotinic acid 3 5% mecholyl[®] chloride 0 9% histamine *diphosphate* and 20% tetraethylammonium chloride in a base of equal parts of petrolatum and lanolin caused no significant digital changes in Raynaud s disease

In view of these pharmacologic results repeated applications *of glyceryl trinitrate ointment were tested in 15 patients* with Raynaud s disease 8 had moderate or pronounced improvement and 7 none Of 10 patients with Raynaud s phenomenon only 1 (with occupational occlusive arterial disease) showed great and 2 moderate improvement Clinical improvement *was only temporary Transient headache ½ 2 hours* after application of the ointment usually disappeared after the ointment had been used for a few days No other unpleasant side effects were noted

Arteriovenous Anastomosis for Peripheral Disease Homer L Skinner and E Finch Parsons (U S Marine Hosp Staten Island N Y) performed 10 shunt operations 9 on seven patients with arteriosclerosis obliterans (with and without diabetes) and 1 *on a patient with thromboangitis obliterans* The procedure consisted of a side to side anastomosis of

(1) N w E J Med 31 1843 1845 A g 1 1951

predisposing to thrombosis who should not receive anti biotics without protection of anticoagulants Especially should patients with phlebitis (unless clearly due to infection) not be given penicillin which would be ineffectual and perhaps dangerous In fact use of such powerful agents as antibiotics against infection is justified only when they are indispensable never as routine

Silicone Tube Coagulation Time as Aid in Diagnosis of Phlebothrombosis is evaluated by Robert S McCleery John A Yarborough and Michael G Weidner Jr[6] (Nashville Tenn) Of 4 836 patients operated on during 2½ years 273 selected as being most likely to have phlebothrombosis were checked before and daily after surgery for silicone tube co agulation time Other hospital patients with signs or symp toms suggesting venous thrombosis were checked making total of 364 patients Fibrinogen B prothrombin time Lee White coagulation time and blood viscosity determinations were also made daily on many of them for comparison

Three precautions are necessary in the silicone tube test (1) venipuncture must be nontraumatic since liberation of a small amount of thromboplastin through trauma greatly shortens coagulation time (2) excessive agitation of the tubes must be avoided and (3) the test must not be made within three hours of intramuscular injection of penicillin Before considering a result positive the authors immediately repeat the test and place the patient at bed rest a third check is made 12 hours later If all coagulation times are 45 minutes or less the result is considered positive and active therapy initiated

Of the 273 patients selected evidence of phlebothrombosis developed in 18 (6 5%) with silicone coagulation times be tween 20 and 45 minutes and leg signs False positive rate was extremely low Normal preoperative coagulation times of the 273 patients varied those for about 75% ranging between 60 and 89 minutes with some as low as 50 minutes and a few as high as 150 minutes Of the seven patients with preoperative times between 50 and 59 minutes three had phlebothrombosis postoperatively suggesting that patients with preoperative coagulation times in this range should be followed carefully with daily postoperative determinations

(6) S g y 31 28 42 J ry 1952

termittent claudication can thus be compared with placebo medication Milton Kissin Julius J Stein and Ralph J Adleman[4] (Beth Israel Hosp New York City) studied patients aged 49 77 with intermittent claudication due to arteriosclerosis Aminophylline was tested on 20 patients all other drugs and placebos on 10 Two to four control measurements before medication were followed by four measurements each 15 minutes apart after the drug (or placebo) had been administered None of the following drugs affected exercise tolerance nitroglycerin (0 4 mg sublingually) papaverine (65 mg in 2 cc solution intravenously or 100 mg orally) alcohol (30 cc of 100 proof Bourbon whisky orally) depropanex® (3 cc intramuscularly) nicotinic acid (100 mg in 10 cc solution intravenously) histidine and ascorbic acid (500 mg sodium ascorbate intravenously and an hour later 0 2 Gm histidine levomonohydrochloride in 5 cc solution intramuscularly and 100 mg sodium ascorbate subcutaneously) paravertebral block (8 cc of 2% procaine solution) and cytochrome C (50 mg in 5 cc solution intravenously) with methylene blue (50 cc of a 1% solution given intravenously 2 cc/minute)

Aminophylline (240 mg in 10 cc solution intravenously given over five minutes) improved exercise tolerance in one third of the patients after one hour and in half of them after two hours Improvement when it occurred lasted at least three to four hours Although the cause of this improvement was not determined it may be due to improved blood flow to the limbs owing to increased cardiac output The authors stress that the tests were acute only therapeutic effects on intermittent claudication were not determined nor was oral administration tried

Thrombogenic Action of Antibiotics and Danger of Their Immoderate Use Penicillin and most other antibiotics seriously affect blood coagulability incidence of thromboses in penicillin treated patients is high Extensive studies have indicated that the antibiotics accelerate blood coagulation J Brehant and Ch Finas[5] (Oran) therefore warn that coagulation time and prothrombin level must be watched during therapy especially in patients with cardiovascular conditions

(4) A g ol gy 2 217 4 J 1951
(5) J se méd 59 1013 J ly 14 1951

predisposing to thrombosis who should not receive anti biotics without protection of anticoagulants Especially should patients with phlebitis (unless clearly due to infection) not be given penicillin which would be ineffectual and perhaps dangerous In fact use of such powerful agents as antibiotics against infection is justified only when they are indispensable never as routine

Silicone Tube Coagulation Time as Aid in Diagnosis of Phlebothrombosis is evaluated by Robert S McCleery John A Yarborough and Michael G Weidner Jr [6] (Nashville Tenn) Of 4 836 patients operated on during 2½ years 273 selected as being most likely to have phlebothrombosis were checked before and daily after surgery for silicone tube co agulation time Other hospital patients with signs or symp toms suggesting venous thrombosis were checked making total of 364 patients Fibrinogen B prothrombin time Lee White coagulation time and blood viscosity determinations were also made daily on many of them for comparison

Three precautions are necessary in the silicone tube test (1) venipuncture must be nontraumatic since liberation of a small amount of thromboplastin through trauma greatly shortens coagulation time (2) excessive agitation of the tubes must be avoided and (3) the test must not be made within three hours of intramuscular injection of penicillin Before considering a result positive the authors immediately repeat the test and place the patient at bed rest a third check is made 12 hours later If all coagulation times are 45 minutes or less the result is considered positive and active therapy initiated

Of the 273 patients selected evidence of phlebothrombosis developed in 18 (6 5%) with silicone coagulation times be tween 20 and 45 minutes and leg signs False positive rate was extremely low Normal preoperative coagulation times of the 273 patients varied those for about 75% ranging between 60 and 89 minutes with some as low as 50 minutes and a few as high as 150 minutes Of the seven patients with preoperative times between 50 and 59 minutes three had phlebothrombosis postoperatively suggesting that patients with preoperative coagulation times in this range should be followed carefully with daily postoperative determinations

(6) S ge y 31 28 42 J ry 1952

Of all the tests only the silicone coagulation time seemed to have diagnostic value in the clinical problem of phlebothrombosis and pulmonary embolism Even it had no predictive value since the result was normal the day before the disease appeared Its merit appears to be early diagnosis Three days from onset of thrombotic disease clotting time may again be normal Low silicone coagulation times were found only in phlebothrombosis In all of 25 patients with thrombophlebitis clotting time was normal

Response of Dicumarol Induced Hypoprothrombinemia to Vitamin K_1 was studied in 62 patients by Alfredo Rehbein Alfred Jaretzki III and David V Habif[7] (Columbia Univ) An emulsion containing 50 mg /ml vitamin K_1 was used Particle size under the phase microscope was less than 1μ The emulsion stable and effective after four months when protected from light and found safe for intravenous administration reversed hypoprothrombinemia due to dicumarol* and the other available prothrombin depressing drugs—tromexan phenylindanedione and compound 63 Doses of 50 mg consistently returned elevated prothrombin time to or near normal in about six hours irrespective of degree of hypoprothrombinemia and amount of recently administered prothrombin depressing drug Generally this dose also maintained prothrombin time at normal levels without subsequent rebound After excessive amounts of a prothrombin depressing drug the 50 mg dose may have to be repeated at 6-12 hour intervals for several doses Normal response to later dicumarol* therapy may be expected after 50 mg vitamin K_1

Vitamin K_1 emulsion controls bleeding due to dicumarol* induced hypoprothrombinemia by permanently correcting the coagulation defect more rapidly than any other agent Use of whole blood and plasma is obviated except when blood volume replacement per se is required Large doses of the water soluble preparation of vitamin K require 12-48 hours and often longer to correct coagulation defect Doses of 0 5 2 5 mg vitamin K_1 return a high prothrombin time to a safe therapeutic range when small doses of dicumarol* have been administered

Recurrent Thrombophlebitis in Obscure Malignant Tumor of Lung Report of Four Cases in which thrombophlebitis

(7) A n S rg 135 454 469 Ap 1 195

antedated recognition of primary pulmonary neoplasm and failed to respond to adequate anticoagulant therapy is presented by Martin M Fisher Lew A Hochberg and Nathan D Wilensky[8] (Kings County Hosp Brooklyn) Three patients had recurrent thrombophlebitis and had once been thought to have thromboangiitis obliterans

CASE 3—Man 42 had pain and intermittent claudication in the right leg for 10 days Physical examination and oscillometric readings showed no abnormalities evidence of thrombophlebitis or symptoms referable to the chest Three months later he returned with thrombophlebitis and swelling streaking and a palpable vein evident in the left leg Despite typhoid therapy a week later streaks were noted on th inner a pect of the right elbow and l ft ankle thrombophlebiti sub ided after four more days

A month later he complained of pain in the right side of the chest Fluoroscopy showed elevation of the right dome of the diaphragm Two weeks later he had a right pleural effusion which produced dyspnea The chest was tapped and 250 cc fluid removed Cell block examination showed anaplastic lung carcinoma Chest x rays after fluid removal revealed a definite mass 8 cm in diameter in the right middle and upper lobes of the lung

CASE 4—Man 66 had painful swelling of the right ankle for three months He had calf tenderness and a positive Homans sign After 2½ months cough and dyspnea developed and lung carcinoma was diagnosed X rays showed a 10 5 cm mass in the left lung Diagnosis was confirmed on pneumonectomy Follow up for nine months was uneventful

Recurrent thrombophlebitis in men is a warning sign of hidden carcinoma Clinically superficial thrombophlebitis lesions coupled with carcinoma are characterized by thrombosis with little evident inflammatory reaction they subside in a few days With the second attack regardless of location mildness or brevity thorough study should rule out lung cancer In many patients previously thought to have recurrent idiopathic thrombophlebitis persistent study would have shown latent visceral cancer If adequate anticoagulant therapy fails to prevent further thromboembolic phenomena cancer should also be suspected

Treatment of Aneurysms with Fibroblastic Agents Experimental and Clinical Studies with Use of Sodium Dicetyl Phosphate Jacob K Berman and James E Hull[9] (Indianapolis) injected aqueous solutions into the adventitia of the abdominal aorta of four rats All made satisfactory recovery

(8) J A M A 147 1213 1 16 N 24 1951
(9) S g Gy & Ob t 94 543 549 M y 1952

After four weeks laboratory studies showed dilatation above the injection site or constriction below The experiments indicated that solutions up to 10% are safe producing practically no destruction of tissue cells and inducing fibroplasia slowly in four weeks Experiments in dogs indicated that a 2% aqueous solution may be injected periarterially without untoward or toxic effects and with resultant fibroplasia Reaction equaled that obtained with 0 9% solution of dicetyl phosphate suspended in olive oil

To treat aneurysms of arteriosclerotic and syphilitic origin in man a 2% aqueous solution was prepared and autoclaved at 240 C with 15 lb pressure for 20 minutes Injections were made through a 21 gauge needle Needles of various lengths were used and the curve in the lumbar puncture needle was shaped to follow the curve in the aneurysm Patients in whom the aneurysm wall was not dissected showed clinical improvement after perisaccular injection The material was definitely nontoxic and induced fibroplasia equal to that of cellophane wrapping It has in its favor ease simplicity and safety of administration Perhaps its greatest usefulness will be as an adjunct to such therapy as partial ligation or the introduction of wire In the following instance olive oil solution was used

Man 49 had a large aneurysm of the ascending aortic arch which constricted the trachea and esophagus and produced paralysis of the right vocal cord Wassermann reaction was 4 + For several months he had slept in a sitting position A dose of 100 cc sodium dicetyl phosphate 0 9% solution in olive oil was injected around the aneurysm Eight weeks later he could sleep lying down and swallow without discomfort and after three months returned to work as truck driver One year later he was killed Autopsy revealed a large saccular aneurysm of the ascending aorta (7 cm in greatest diameter) The walls contained organized clots scar tissue and calcific deposits Actual diameter of the lumen through which free blood could flow within the sac was narrowed at points by larger clots to almost normal The aortic ring was moderately dilated (8½ cm circumference) The other great vessels were grossly normal The aneurysm was intact at all points with no apparent weakening or rupture

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MISCELLANEOUS

The Myth of Strict Bed Rest in Treatment of Heart Disease is attacked by Samuel A Levine[1] (Harvard Univ) The rationale of bed rest is to decrease the work of the heart

(1) Am H a t J 42 406 415 S pt mber 1951

However in actual or incipient congestive heart failure the work of the right ventricle may actually be increased as shown by a decrease in vital capacity and slowing of blood flow Similarly in patients with hypertensive heart failure recumbency for a day or two leads to hemodilution increased blood volume increased venous pressure and decreased vital capacity all of which increase the load on the heart

On the other hand patients with congestive heart failure in whom all other measures had failed had dramatic relief of dyspnea and pulmonary edema with chair treatment [see Levine and Lown this YEAR BOOK p 402] It is suggested that a sitting posture mobilized the pulmonary edema fluid into the legs where it causes less harm and fewer symptoms In addition to psychologic advantages chair treatment permits a smoother and more gradual convalescence reduces the burden on the hospital nursing staff simplifies treatment at home and results in better preservation of bladder function

Among 75 hospitalized patients severely ill with myocardial infarction who had the chair treatment in addition to the customary methods 7 died Pulmonary edema and dyspnea only rarely developed and ventricular rupture occurred only once Hypostatic or bronchopneumonia and thrombophlebitis with its complication of pulmonary embolism are less likely It seems too early to state the long range effect of this treatment but the results so far have been encouraging and are advocated for routine use in management of myocardial infarction and all forms of congestive heart failure

[The psychologic advantage of avoiding strict rest in bed must be strongly emphasized Many patients with myocardial infarction become so frightened by the physician's insistence on prolonged and complete rest in bed that they develop a permanent anxiety state Such a condition when severe may cause more suffering and more economic disability than the average instance of organic cardiac disease

From the physical point of view there is an advantage in having fluid and excess blood accumulate in the legs rather than in the lungs The editor therefore agrees with the opinions expressed here —Ed]

Study of 175 Cardiacs without Heart Disease found among 631 patients is reported by Leonard J Goldwater Lewis H Bronstein and Beatrice Kresky (Columbia Univ) There was a preponderance of males under 35 The largest single group comprised 38 patients given a diagnosis of heart disease on routine examination for the armed forces Among

(2) J A M A 148 89 92 J 12 195

the 60 patients who originally consulted physicians the commonest symptoms had been fatigue dyspnea precordial pain and palpitation, some had had noncardiac symptoms and a few had sought medical advice because of anxiety about the heart A few with symptoms that they attributed to the heart had been told but not convinced that there was no cardiac abnormality Several others after learning they had a murmur were not assured of its benign nature This rejection of the favorable and readiness to accept the unfavorable was a prominent manifestation of the anxiety shown by about half the patients

Erroneous diagnosis of heart disease was usually due to faulty interpretation of signs and symptoms present at some time although some patients had no history of abnormality Many had merely been told after routine examination that something was wrong with the heart Since most of them had had no abnormal symptoms it must be presumed that a murmur or an irregularity of rhythm had been found A clue to the misdiagnosis was found in about half the cases Heart murmurs interpreted by the authors group as being purely functional accounted for 44 cases Essential hypertension uncomplicated by demonstrable cardiac involvement accounted for 11 and diseases other than heart disease (including thyrotoxicosis pulmonary tuberculosis gastrointestinal neoplasm and late latent syphilis) were diagnosed in 22 cases

Limitations had been advised for 56 persons but only 19 had obeyed them Of the 31 persons who limited activities 7 did so without or despite a physician s advice Many of those who contrary to advice had not observed restrictions had consequent emotional conflict At least 17 different kinds of restrictions impo ed on the 56 patients ranged from take it easy to restrictions for the completely disabled At examination 70 patients were working of the 105 not working 25 were idle because of a physician s advice and so attributed unemployment to heart di ease and 68 ascribed idleness to noncardiac causes Among the latter inability to find a job was often inability to find one which would not subject them to excessive physical exertion Many of the jobless being certain of rejection did not apply in establishments known to require a pre employment examination

Effects of Tubing Bore on Stethoscope Efficiency was studied by Maurice B Rappaport and Howard B Sprague[3] (Boston) by means of a sound pressure meter and other devices They previously showed that the efficiency of a stethoscope increases as tubing length is decreased If the tubing is made too short the stethoscope becomes difficult to handle A 10 in length of rubber tubing is optimal for handling

Equal lengths of rubber tubing 1/4 3/64 in in caliber were tested Tubing with a 1/8 in bore was most efficient from about 115 down to 40 c that with a 3/64 in bore was most efficient from 20 to 40 c but above 40 c efficiency dropped rapidly The following auscultatory sounds generally fall in the low frequency portion of the spectrum (20 115 c) mitral diastolic murmurs low pitched basal diastolic murmurs first second and third heart sounds some systolic murmurs and the auricular sound The usual commercial stethoscope tubing (3/16 in bore) was less efficient between 20 and 115 c by an appreciable number of dynes/sq cm of sound pressure which is applied to the observer s ears Between 200 and 750 c the difference in efficiency was not as large although the 1/8 in tubing seemed to have a slight advantage This portion of the auscultatory spectrum includes the high and medium pitched murmurs Above 750 c the tubing with the 1/4 in bore became most efficient and the 3/64 and 1/8 in tubings least This portion of the frequency spectrum has negligible utility in cardiac auscultation Rales do have some frequency components in this portion of the spectrum

A 1/8 in bore in the metal binaurals instead of the usual 3/16 in further increases stethoscope efficiency

Diagnostic Value of Cardiac Auscultation. According to Samuel A Levine[4] (Harvard Med School) much easily obtainable information is overlooked by inadequate auscultation Three types can be obtained by it (1) In the absence of a murmur certain diagnoses may be dismissed such as bacterial endocarditis (2) Definite diagnosis may be established Pericardial friction almost invariably means acute pericarditis a diastolic or presystolic apical rumbling murmur is diagnostic of mitral stenosis a faint early diastolic murmur at the

(3) Am H rt J 42 605 609 O tobe 1951
(4) C n J M d 33 7 77 M r h 195

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ing such as second and third degree heart block Detection of these changes in intensity ot the first sound is the only reliable bedside method of making these diagnoses

Althouth in auricular and ventricular paroxysmal tachy cardia the heart rate may be regular and rapid (160 200) in the former the auricles are contracting at the ventricular rate and at a constant short interval before the ventricles That should result in first heart sounds of uniform intensity In the latter the auricles generally contract independently and at a slower rate than the ventricles which should result in changing intensity of the first sound Clinical experience bears out these predictions The distinction between these types of paroxysmal tachycardia which may be made by simple auscultation is exceedingly important Digitalis so commonly used in cardiac emergencies with rapid heart rate is harmful in ventricular tachycardia whereas quinidine is often effective and may be life saving

Management of Cardiac Patients in Relation to Surgery is discussed by A Carlton Ernstene[5] (Cleveland Clinic) Usually in a patient with heart disease about to undergo surgery clinical history and physical examination are suf ficient to decide whether the operative risk is greater than u ual cardiac reserve is insufficient there is danger of sudden death due to the heart condition the heart disease should be treated preoperatively the cardiac condition allows only emergency and palliative surgery certain ane thetic agents are contraindicated and cardiovascular complications can be anticipated Anoxia and hypotension are the greate t dangers and if avoided patients essentially symptom free tolerate operation with no extra hazard Except in a patient with decreased myocardial reserve an abnormal ECG per se does not contraindicate surgery and general anesthesia If con gestive heart failure is present operation should be delayed if possible until full digitalization and other routine measures have been taken If auricular fibrillation is present ventricular rate should be decreased to about 70 beats/minute Digitaliza tion is also advocated for patients without congestive failure but with exertional or paroxysmal nocturnal dyspnea on a cardiac basis When the heart disease has severely limited life expectancy elective surgery should not be undertaken

(5) C 1 t 4 430 436 S pt mb 1951

base indicates early aortic insufficiency In some cases no other reliable method aids diagnosis of slight mitral stenosis or aortic insufficiency (3) Diagnostic clues may be discovered A patient may be stricken with severe epigastric pain resembling acute pancreatitis and the heart may show a classic diastolic gallop This would suggest the heart as the cause of pain At times a hyperactive first sound not explicable otherwise may suggest that thyrotoxicosis is present

Gallop rhythm is too often overlooked When the third sound of a gallop can be identified in diastole it almost always indicates fairly grave heart disease In some comparatively benign gallops the extra sound occurs during systole In fact a midsystolic gallop is often detected in persons without heart disease Generally the types may be distinguished by auscultation only occasionally are graphic methods required

Heart sounds may be decreased in intensity with severe emphysema large pericardial effusion or extreme obesity and in moribund patients both heart sounds are similarly muffled The situation is entirely different when the first heart sound is decreased and the second is not The first sound is due mainly to closure of the mitral and tricuspid valves The abruptness of ventricular systole affects the first sound When the contraction is hyperactive as in hyperthyroidism anemia or certain fevers (especially acute rheumatic fever) the first sound is often accentuated The valve leaflets close more abruptly and a brisk sound results Experimentally it has been inferred that when the mitral and tricuspid leaflets are wide apart the instant the ventricles contract the sound produced as they close will be different (probably louder) than when they are nearer together If the ventricles contract soon after the auricles the sound will therefore be loud if there is delay between auricular and ventricular systole the valves will have had a longer opportunity to float upward and nearly close and the first sound will be faint Clinical experience shows that attention to intensity of the first sound as heard at the apex often enables the observer to estimate length of the P R interval and to recognize conditions in which there is a short one others with a prolonged one (first degree heart block) and those in which this interval is vary

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(5) C c l t 4 430 436 S pt mb r 1951

when it is secondary as in hyperthyroidism subtotal thyroidectomy may be done after careful preoperative medical treatment

Cyclopropane is not recommended for patients with organic heart disease because of the danger of inducing ventricular arrhythmias if it is used epinephrine must not be given Simultaneous administration of atropine and prostigmin is also contraindicated

If ventricular arrhythmias are present or need to be prevented 100 500 mg pronestyl should be given intravenously Cardiac arrest or ventricular fibrillation can be dealt with if immediately recognized and treated with massage and defibrillation in that order Intracardiac injection of epinephrine *may cause ventricular fibrillation in cases of cardiac standstill* However it may be used (1 cc of 1 1000 solution injected into the right auricle or ventricle) after massage has restored a definite but feeble heart beat

Intravenous administration of fluids containing sodium should be avoided Liberal use of antibiotics early ambulation and use of anticoagulants in phlebothrombosis have greatly reduced postoperative complications

Clinical Evaluation of Ballistocardiogram II Heart Disease—Hypertension, Angina Pectoris and Myocardial Infarction Kenneth Chesky Marvin Moser Robert C Taymor Arthur M Master and Leon Pordy[6] (Mount Sinai Hosp New York City) investigated 135 patients using the ballistocardiograph described by Dock and recording simultaneously with an electrocardiograph

Among 50 hypertensives of 40 patients with hypertensive heart disease only 1 had a normal ballistocardiogram at rest Commonest abnormalities were a small or absent I and deep K waves Only one patient with early but definite hypertensive heart disease had a normal ballistocardiogram at rest All 10 with essential hypertension had normal ECG s but 9 had abnormal ballistocardiograms (small I and deep K waves) Eleven of 18 hypertensives with normal resting ECG s had abnormal ballistocardiograms at rest and after exercise whereas the ECG s remained normal in 8 after the double two step exercise test

Among 45 patients with normal resting ECG s but positive

(6) Am Heart J 42 3 8 333 September 1951

response to the two step exercise tolerance test 10 had normal resting ballistocardiograms The others had such abnormalities as small or absent I waves or abnormal J K egments Six of the 10 were exercised after which 2 now had an abnormal tracing In addition a borderline balli tocardiogram at rest became definitely abnormal with exercise

There were 40 patients with myocardial infarction At the time of the study four had a normal ECG but abnormal ballistocardiogram However three patients had a normal ballistocardiogram although the ECG was abnormal Again small or absent I waves and abnormal J K segments were the most frequent abnormal patterns

The authors believe ballistocardiography is a helpful addition to other clinical and laboratory methods for evaluation of cardiac function and reserve in routine clinical practice

[The editor disagrees with this conclusion The Dock ballistocardiograph is a tool of great promise but is still subject to many artefacts Until these are overcome and a satisfactory generally accepted standardized procedure has been developed the ballistocardiograph should be regarded as a tool for research rather than for routine clinical use The mechanism of production of some of the various waves is poorly understood Ballistocardiographic interpretation i on a purely empir c basis

A comparison may be drawn with the electrocardiogram Every experienced cardiologist sees numerous patients who have had false positive d agnoses of heart disease through overempha is on minor electrocardiographic changes This is still occurring despite three or more decades of experience with this instrument despite the relative simplicity of the records and despite the investigations of the Wilson school wh ch have clarif ed the genesis of the various waves When we consider that the ballistocardiograph is a much more recent tool yields more complex tracings and is subject to many more artefacts than the electrocardiograph, one shudders at the thought of the diagnostic and therapeutic errors which would probably result from its wide pread routine use at the present t me On the other hand it appears that the in trument may in the long run have as great or greater practical value than the electrocardiograph This will not come about until much more research has been done on the genesis of the waves normal var ations problem of standardization means of avoiding artefacts etc —Ed]

Air Embolism is discussed by Archibald C Cohen George C Glinsky[7] (Butler Pa) George E Martin and K I Fetterhoff (Pittsburgh) Arterial air embolism is usually a complication of artificial pneumothorax thoracentesis or thoracic surgery Air is either injected accidentally during the procedure or venous pathways are opened and air sucked into them before clotting can occur since the pressure in the veins is below atmo pheric and the pressure in the air pas ages

(7) A n I t M d 35 779 84 Oct be 1951

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(6) Am H a t J 4 3 8 333 S pt mbe 1951

amount of air reaching the circulation speed with which it enters and position of the body when embolism occurs Treatment consists chiefly of putting the patient in the left lateral position which favors displacement of the air trap and relief of the obstruction Ventricular puncture and aspiration of air have been reported Shock should be combated

Acute Benign Pericarditis O F Rosenow and C J Cross[8] (Columbus O) report on four patients aged 26-52 Typical signs and symptoms differentiating the condition from myocardial infarction are sharp often severe substernal or precordial pain of sudden onset aggravated by deep breathing friction rub fever occasional history of respiratory infection early leukocytosis and increased sedimentation rate and alterations in serial electrocardiograms

All four patients presented characteristic signs and symptoms A shocklike picture was present in some degree Two patients had no contributory histories but the other two had had a respiratory infection presumably of virus origin These two were treated with terramycin or aureomycin with immediate symptomatic relief but ECG changes and sedimentation rate remained abnormal as long as in the two controls

Close clinical observation suggestive laboratory findings and diagnostic ECG s are important in differentiating this condition from myocardial infarction Complete early recovery is the rule

Acute Idiopathic Pericarditis Ralph C Parker Jr and Henry R Cooper[9] (U S Nav Hosp Bethesda Md) report on 22 cases The major findings of acute pericarditis (chest pain pericardial friction rub electrocardiographic changes and x ray evidence of cardiac enlargement) were frequently found The chest pain present in 95% varied considerably In most patients it was aggravated by movement breathing or coughing a semiupright position minimized it In half the cases pain recurred in a number of instances it was accompanied by a febrile response and an exacerbation of associated pneumonitis Electrocardiographic changes indicative of pericarditis were found in all patients Pericardial friction rub

(8) A M A A h I t Med 87 795 807 J 1951
(9) J A M A 147 835 839 Oct 27 1951

atmospheric Arterial air embolism also occurs regularly in caisson disease Since a little air can completely block an important artery, only a few cubic centimeters may be fatal if it reaches a cerebral or coronary artery Air entering the cerebral circulation may cause such neurologic manifestations as aphasia blindness hemiplegia or convulsions and ophthalmoscopy *may reveal air bubbles in the retinal arteries* A marbled appearance of the skin suggests air in the superficial vessels and is often found in the superiorly located portions of the body A small incision in the skin of the upper part of the body may show that the blood contains air bubbles (air bleeding) Myocardial infarction has been demonstrated by electrocardiography and at autopsy Treatment is postural and supportive The head should be lowered at once This will not prevent emboli from reaching the coronary circulation nor dislodge air bubbles already present in the cerebral circulation but will prevent any more air reaching the brain If necessary external heat should be applied treatment for shock given and convulsions controlled

Venous air embolism may result from faulty technic in intravenous injections or from infusions It is a rare complication of operations when a vein with a negative pressure is cut The uterine sinuses have been the point of entry of air during delivery pelvic operation vaginal insufflation of air for trichomonas infestation and transuterine air injections The veins of the neck chest and dural sinuses have been incriminated in a few cases The condition has in some cases followed injections of air into the peritoneal cavity

If there is enough air there is a sensation of bubbling in the left chest over the pulmonary conus at the same time air in the right ventricle produces a churning sound (mill wheel murmur) often audible without a stethoscope An air trap forms in the right ventricle causing obstruction which causes elevated venous pressure cyanosis often syncope through cerebral anoxemia and forward cardiac failure with deficient cardiac output and rapid feeble pulse Some air may pass through the right heart into the lungs to cau e embolism of small and medium sized pulmonary arteries Symptoms are dyspnea hypernea and tachypnea sometimes so severe that alkalosis and tetany develop Prognosis depends on the

Nathan J Kursban and Arnold Iglauer[1] (Jewish Hosp Cincinnati)

Woman 28 had substernal distress which began while eating She denied any previous symptoms Intensity of pain varied but was worst during the fir t 24 hours It was felt chiefly over the lower third of the sternum and was relieved by rest Two days later chills and fever developed Despite antibiotics fever of 99.2 104 F persisted On hospitalization temperature was 101 F pulse 120 and respiration 22 There were no venous distension petechiae or nodules The pharynx was clear Blood pressure was 120/80 Apical impulse was palpable in the midaxillary line and was fairly strong A har h friction rub was audible along the left bord r of the sternum and farther to the left Chest examination was normal except for slightly restricted expan ion of the left side Abdomen and extremities were negative *Laboratory studies including anti* hyaluronidase titer were not remarkable Chest x rays showed somewhat enlarged heart hadow in the transverse diameter (16 cm in a 28 5 cm che t) Shape v is not characteri tic Lung fields were clear *Fluoroscopic and roentgen kymographic examinations* revealed diminish d pulsations particularly over the left ventricular segment Electrocardiogram showed low T waves in limb leads and inversion of T in V_1 V and V_4 and was con i tent with subacute peri arditis

The patient s fever lasted 16 days despite p nicillin chloram phenicol and aureomycin therapy and adequate do es of salicylates *Pericardial fric ion rub vas continuous Teleroentgenograms* showed an increase of 1 5 cm in th transver e diameter of the cardiac shadow when ACTH therapy was instituted on the 16th day of illnes Sodium intake was restricted to 1 000 mg /day and 1 Gm *pota sium chloride* was given three times daily After 24 hours of ACTH therapy temperature dropped to normal chest soreness dimini hed markedly and appetite and sense of well being promptly improved ACTH 100 mg /day was given for six days and then reduced to 40 mg /day for three days after which the drug was continued at home (10 mg twice daily for five days) with apparently complete remis ion The pericardial rub diminished markedly after two days of ACTH and disappeared after five days Chest x ray one month after onset showed diminution in transverse diameter of the cardiac shadow

Subacute Bacterial Endocarditis L N Roberts and W Goldberg (Victoria Hosp London Ont) stress the impor tance of early accurate specific identification of the responsi ble organism and determination of the antibiotic to which it is most sensitive and in what concentration

CASE 1—In a woman 41 various antibiotics were tried but only terramycin orally and aureomycin intravenou ly apparently were

(1) Oh M J 47 915 918 Oct b 1951
( ) C d M A J 65 53 55 J ly 1951

lasting from a few hours to two or three weeks was noted in 45% In all severe cases a friction rub was heard Demonstrable enlargement of cardiac silhouette subsequently returned to normal in 68%

Pneumonitis was present in 64% Of 13 patients with x ray evidence of pneumonitis 7 had pleural effusion Generally leukocytosis and a shift to the left were noted All had fever generally moderate for one day to three or four weeks Two or three febrile exacerbations lasting 7 10 days each occasionally characterized the course This complicates evaluation of the role of antibiotics and chemotherapy At least half the patients were given sulfonamides penicillin or streptomycin without definite effect

Differential diagnosis concerns mainly acute coronary thrombosis other types of pericarditis myocarditis and such other causes of chest pain as pleurisy spontaneous pneumothorax and pulmonary infarction and occasionally acute abdominal conditions Diagnosis is largely based on exclusion In the early hours acute coronary thrombosis pain may be difficult to differentiate but important indications of acute idiopathic pericarditis are (1) variation of the pain with thoracic movements (2) early pericardial rub (3) associated pneumonitis and (4) no reciprocal S T segment depressions Later cardiac enlargement without Q waves or QRS abnormalities often prolonged fever and usually rapid return to normal ECG pattern aid in diagnosis

Most commonly considered in differential diagnosis is rheumatic pericarditis In a reported series of pericarditis in young adults all 25 patients with rheumatic fever had preceding or concomitant joint symptoms and 9 had first or second degree heart block Neither joint pains nor heart block was found in any of 15 patients with apparent idiopathic disease Murmurs erythema marginatum rheumatic nodules and the usually more protracted course may aid in differentiation Tuberculous pericarditis may be difficult to differentiate but the effusion is characteristically slow to develop and massive in quantity Other evidence of tuberculosis is ordinarily found or develops subsequently Pericarditis with concomitant rheumatoid arthritis is difficult to differentiate

Acute Nonspecific Pericarditis Report of Case Treated with ACTH (Adrenocorticotrophic Hormone) is presented by

curred after the reaction appeared to be subsiding therefore patients should be carefully watched for at least two hours

Almost routinely the ECG s showed flattening of T waves at the height of reaction In four there were significant altera tions One was a patient with no symptoms other than a blush and mild sensation of warmth blood pres ure remained at the initial level but the ECG showed frequent premature ventricular beats In one patient the ECG recorded shifting sinus and nodal rhythm with periods when P waves were absent Two showed changes suggesting myocardial ischemia One patient had a myocardial infarction after ingestion of a bottle of ale while outside the hospital

Potassium Lack in Postgastrectomy Dumping Syndrome W Hamilton Smith[4] (Postgraduate Med School) studied six patients four with partial gastrectomy two to four years previously one total gastrectomy with esophagojejunostomy seven years before and one vagotomy four years previously Postprandial attacks (with palpitation and muscular weak ne s) often occur after gastrectomy either within ½ hour or 1½ 3 hours after meals The former are thought to be due to rapid gastric emptying (dumping) and the latter to hypo glycemia

The patients and four normal controls were studied before and after a standard meal During the meal or within 30 minutes of its beginning abdominal discomfort often nausea palpitations weakness and drowsiness were noted Moderate increase in heart and respiratory rate and blood pressure pallor and sweating were also observed presumably due to release of an epinephrine like vasoconstrictor

Serum potassium levels in the controls were unaltered but fell in patients with dumping attacks together with rise in blood sugar value and abnormal fall in serum inorganic phosphorus value Electrocardiograms made during the phase of weakness and lowered potassium concentration showed changes characteristic of hypopotassemia In two patients dynamometer tests made during attacks showed a response decreased by 20% In the two patients tested electromyograms showed reduction in action potentials of 20 and 13%

One patient was given a total of 21 4 mEq potassium intravenously over 90 minutes beginning an hour before the

(4) La t 2 745 749 O t 27 1951

effective against Streptococcus zymogenes Terramycin had to be discontinued because of toxic symptoms (nausea and vomiting) after nine days on 5 capsules of 250 mg every six hours Aureomycin was given intravenously continuously for 26 days (2 000 cc of 5% glucose in distilled water daily containing 600 mg aureomycin and 200 mg heparin given through a plastic venous catheter) Temperature and sedimentation rate returned to normal and blood cultures showed no growth for two months after cessation of treatment

CASE 2—In a man 55 Streptococcus faecalis was the infecting organism Original dosage was 1,200 000 units of penicillin 2 Gm dihydrostreptomycin and 2 Gm aureomycin daily but after a week was increased to 1 000 000 units of penicillin every three hours and 2 Gm streptomycin and 3 Gm aureomycin daily and maintained for many weeks When discharged the disease had been arrested clinically (last positive blood culture five months previously) and he had received a total of 1 224 000 000 units of penicillin 318 Gm streptomycin and 504 Gm aureomycin

It is apparent that massive dosage of combined antibiotics may be necessary in treatment of these infections

Cardiovascular Complications of Tetraethylthiuramdisulfide (Antabuse®) Treatment of Alcoholism Edward A Macklin Maurice Sokolow Alexander Simon and William Schottstaedt[3] (Univ of California) treated 82 problem drinkers after extensive examination with particular emphasis on the cardiovascular system to eliminate possibility of physical disease Medication was started routinely with doses decreasing from 1 Gm the first day to a total of 4 Gm in the first five days On the fifth day the first alcohol test was made with 0 5 ml 90 proof whisky/kg body weight Electrocardiograms during alcohol trials were made for 55 patients Blood pressure pulse and respiratory changes during the reaction were recorded in all

Diastolic pressure was decreased to less than 50 mm Hg during the routine alcohol trials in 16 of whom 3 had significant ECG changes in two suggesting myocardial ischemia and in one showing shifting sinus and nodal rhythm with short intervals when no P waves were evident Twelve complained of dyspnea one of the four who did not complained of tightness in the throat and the ECG gave evidence of myocardial ischemia Only three had actual chest pain though several had chest discomfort Ephedrine regularly caused rapid rise in blood pressure and was the most effective treatment for hypotension Secondary falls in blood pressure oc

(3) J A M A 146 1377 1381 Ag 11 1951

stenosis Postoperative arterial oxygen saturation in the living patients studied was well over 90% whereas 70 80% is usually obtained by a shunt procedure

Mitral disease is the commonest of the clinically important valvular involvements Probably 50% of patients present pure mitral stenosis with no insufficiency The stenosis produces stiffening in the zone of valve contact or approximation the valve becoming fixed or frozen in position of partial closure Away from the narrowed orifice the tissues become progressively less diseased so that the basal portion of the valve cone or the circumoral soft tissues may be normal Stenosis may be relieved without producing regurgitation by incision of the commissures ot the valve well beyond the encircling scar tissue and out into the thin flexible normal peripheral tissue Ninety seven commissurotomies were performed for mitral stenosis In the most recent year 1950 71 patients were operated on with four deaths Survivors showed varying degrees of improvement from complete restoration of clinical health to no obvious change The degree of improvement was directly related to the pathology present and to the amount of valvular function which the operator was able to restore Thus thin flexible valve cones purse stringed at the apex permit almost complete restoration to normal Heavily calcified greatly distorted valves permit little restoration Ideally there should be no more regurgitation at the end of the procedure than that noted at the beginning (by palpating the regurgitant stream in the heart) This goal is usually obtained and often there is no regurgitation at the end of the procedure Some patients have such a degree of valve dysfunction that even accurate conservative incision of one commissure may produce an unexpectedly large amount of regurgitation Such postoperative regurgitation as well as severe preoperative regurgitation can be corrected by trans ventricular pericardial tamponage

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THE KIDNEY

Pathogenesis of Acute Renal Failure Associated with Traumatic and Toxic Injury Renal Ischemia Nephrotoxic Damage and Ischemuric Episode Jean Oliver Muriel Mac

meal and continuing after it As soon as an attack had fully developed another patient was given 8 4 mEq over 40 minutes and a third 33 5 mEq over 45 minutes The infusions prevented appearance of the usual muscular weakness reversed ECG changes and terminated the attacks prematurely (Control infusion of normal saline solution was ineffective)

Smith concluded that the dumping syndrome is accompanied by fall in serum potassium level which causes muscular weakness and drowsiness and that these disappear when the potassium level has been restored to normal Two factors may contribute to hypopotassemia release of some epinephrine like substance into the blood and abnormally rapid absorption of carbohydrate with rapid deposition of glycogen and binding of potassium inside the glycogen storing cells

Surgery of Valvular Heart Disease Charles P Bailey Robert P Glover and Thomas J E O Neill[5] (Philadelphia) believe that direct surgical relief of pulmonary stenosis is advisable not only in the pure type but also in tetralogy of Fallot as this reduces the number of cardiovascular defects rather than increasing them as in the shunt or anastomosis procedures Valvular and infundibular stenosis are amenable to direct surgery The type of stenosis can often be diagnosed before surgery by angiocardiography and cardiac catheterization but always at operation as soon as the pericardium has been opened In the valvular type a special knife with olivary tip and a diamond shaped blade is passed through the wall of the right ventricle then up into the pulmonary artery dividing the fu ed valve cone into a bicuspid functioning pulmonary valve In the infundibular type a special Brock type punch or a pair of Glover type rongeurs is thrust through a small incision into the right cardiac chamber to resect a portion of the obstruction In limited stenosis of the pulmonary artery above the valve dilation by graduated urethral type sounds a ain passed through the artery via the right ventricle permits adequate enlargement of the lumen In extreme hypoplasia of the artery the direct approach is inapplicable and a hunt operation indicated

Of 19 patients with tetralogy of Fallot operated on by the direct approach 4 died In 10 patients the stenosis was valvular in 6 infundibular and in 3 there was actual limited arterial

(5) D Ch t 20 453 468 November 1951

into the lumen of the disrupted tubule if there are larger vessels tubulovenous anastomoses may form No such damage can conceivably result from a poison reaching the nephrons by the blood stream Its random and patchy distribution suggests that ischemia is the causal factor Under experimental conditions the Schlegel technic rarely shows an over all even reduction of flow through the vascular bed some areas are bloodless others congested

In any instance of fatal acute renal failure the two lesions are found in varying proportions depending on the nature of the renal insult whether toxic circulatory or both In non toxic acute renal failure (from shock crush injury) the insult is purely circulatory a part of general circulatory disturbance which has involved the susceptible area of the renal blood flow Ischemuric episode would well designate this complication In a man poisoned by an uncontrolled amount of corrosive sublimate vomiting and dehydration end in circulatory collapse This differs considerably from the quiet renal failure in a rabbit given moderate intravenous injection of the same substance Lesions in human kidneys are not examples of simple nephrotoxic damage also found as evidences of circulatory disturbances are disruptive tubular lesions of ischemia From this coincidence stems the unity of pathogenesis in that group of acute renal failure which includes such clinically disparate origins as crush injury transfusion reactions obstetric accidents and fatal poisonings

Acute Renal Failure Lower Nephron Nephrosis according to Louis G Welt and John P Peters[7] (Yale Univ) depends largely on (1) some substance which can destroy renal tubular epithelium abetted by (2) anoxia of the renal tissue Both increase in tonicity of body fluids and contraction of extracellular volume may stimulate release of antidiuretic hormone which increases reabsorption of water in the distal tubule and concentrates the solutes in distal tubular urine If the solutes include a noxious agent its increased concentration will promote greater tubular cells Experimental and clinical evidence directly support this Renal insufficiency is more difficult to produce with intravenously administered hemoglobin in well hydrated animals Hemolytic transfusion reaction rarely leads to lower nephron nephrosis in patients

( ) Y J B l & Med 24 19 230 D mbe 1951

Dowell and Ann Tracy[6] (State Univ of New York Brooklyn) studied morphology of human and animal kidneys by various methods including the mounting and staining of dissected nephrons and Schlegel s method for visualizing the pattern of renal circulation by intravenous injection of a fluorescent dye into the living animal They concluded that two kinds of tubular damage may occur in acute renal failure The first is the well known nephrotoxic lesion resulting from even distribution to every nephron of some poison in the blood stream Like many foreign substances it is filtered through the glomerulus and absorbed by cells of every proximal convolution An intracellular concentration considerably above that in the circulating blood is thereby established and renal cells die Neither the basement membrane nor the epithelial cells of other portions of the nephron are visibly affected both escape because with respect to toxic substances they are functionless The tubule lumen below site of actual damage may be filled with products of both the glomerular lesion (coagulated protein in the form of casts) and epithelial destruction

In contrast is the second kind of tubular lesion first recognized in the crush kidney and believed peculiar to the lower nephron Its distribution within the kidneys is entirely random some nephrons often in groups are involved and others are not Any part of the nephron may be damaged One of the commonest sites is the second half of the proximal convolution extending into the outer medulla histologically easily confused with the ascending distal limb of Henle s loop Rarely is any whole nephron segment affected but rather only a short stretch of tubule or a series of isolated spots distributed over several anatomically and functionally different divisions of the nephron In these areas the entire tubule wall including the basement membrane is affected The epithelium within it is dead and desquamated so that continuity of the tubule is disrupted If there are casts at the site of the disruptive lesion (often there are not) they may extrude from the gaping hole in the tubule In the intertubular connective tissue near the rupture an inflammatory reaction commonly occurs with leukocytic infiltration and formation of inflammatory granulation tissue which extends by growth

(6) J Cl I t. 30 1307 1438 D mbe (pt. 1) 1951

the need for transfusions Proper hydration characterized by normal volume and tonicity of body fluids is as important for protecting renal tubular epithelium when sulfonamides other chemotherapeutic agents or blood is administered in medical diseases

Postoperative oliguria frequently ascribed to lower neph ron nephrosis probably results from contracted plasma vol ume hyponatremia or both Adequate correction of these abnormalities encourages renal function to return to normal If such correction fails to induce proper urine flow little is lost This correction need not induce edema although harmful effects of minimal overexpansion of the extracellular com partment seem negligible There is ample evidence that reason able fluid excess is preferable to dehydration

Regeneration of tubular epithelium is evident by the fourth or fifth day In two weeks it is largely restored and function ing in a few months it may be impossible to detect any signs of the injury Should the patient survive other injuries the renal lesions will be repaired After circulatory efficiency and volume and sodium concentration of body fluids are re stored only current losses should be replaced Potassium con centrations at cardiotoxic levels can be reduced with carboxylic ammonia exchange resin administered orally or instilled per rectum Carbohydrate in 100 Gm doses spread over 24 hours will provide maximal protein sparing and retard rate of ac cumulation of nitrogenous end products and potassium Ab solutely nothing should be given orally until there has been no vomiting or nausea for at least 24 hours If this is meticu lously observed tubes and suction are unnecessary and extra renal losses of fluid and electrolytes with be minimized

Prerenal Proteinuria —I *Particle si e*—T Addis Evalyn Barrett L G Poo and Helen Ureen[8] (Stanford Univ) injected varying quantities of proteins of known molecular weight into the peritoneal cavities of groups of six female albino rats of 150 Gm average weight Each rat was placed in a special cage designed for the collection of urine After 17 hours the urines of each group were combined for determination of the rate of protein excretion During the period of urine collec tion the animals were given ad lib a 35% solution of dextrose

(8) A M A A h I t M d 88 337 345 S pt mbe 1951

with inability to concentrate urine Adequate hydration may modify or prevent lower nephron nephrosis after a hemolytic reaction Increased damage results from dehydration in acidosis and not from acidosis per se Infusions of alkaline solutions in hemorrhagic shock are not strikingly beneficial and may be related to effects on volume and tonicity of body fluids rather than to acid base balance

The degree to which loss of blood volume is compensated by fluid moving from the interstitial space into the blood stream is partly conditioned by the volume of interstitial fluid Contracted plasma volume in dehydration even with no hemorrhage may in itself lead to a compensatory vasoconstriction in the kidney producing renal ischemia and anoxia The anoxia may in itself produce severe acute renal insufficiency potentiating the effect of other nephrotoxic agents A patient at operation is often hydropenic with near maximal antidiuretic activity with urine flow at about 0 5 cc./minute Also during major surgery under general anesthesia in average climatic conditions he may lose 2 4 L fluid through the skin and respiratory passages General anesthesia is in itself antidiuretic The two stimuli which call forth antidiuretic activity—increase in tonicity and contraction of the body fluids—co exist Fluid losses may in themselves promote peripheral vascular collapse commonly treated with transfusion of whole blood In long operations fluid loss increases and many transfusions may be necessary Each transfusion carries with it the hazard of a hemolytic reaction Should one occur it happens when hemolytic products are at maximal concentration in the distal tubules and when these tubules may have endured anoxia secondary to renal vasoconstriction So far as proper hydration can modify the picture it prevents or minimizes this type of lower nephron nephrosis Inordinate volumes of fluids need not be given but enough saline and glucose solution should be used initially to compensate for antecedent losses Continuous intravenous infusion of 5% glucose in water and some saline regulated to promote excretion of reasonably dilute urine and to compensate for sweat and blood losses will protect against concentration in the distal tubule of a substance toxic to the renal tubular epithelium Preliminary provision of these fluids may reduce

globulin) showed a decrease in albumin suggesting that the abnormal part of the albumin had become attached to the added gamma globulin and an increase of the alpha and beta globulins It seems likely that some cementing or solubilizing substance present in normal serum might be lacking in the serum of patients with prerenal proteinuria This may be present normally in the gamma globulin

Benign and Pathologic Albuminuria Study of 600 Hospitalized Cases S Edward King and Christian Gronbeck Jr [1] (U S Army Hosp For Jay N Y) studied 600 draft examinees with albuminuria found in three specimens on two days Ages ranged from 17 to 32 with most subjects in the 17 21 group

After hospitalization all patients were studied according to the following routine The first urine specimen was taken at 8 p m and the patients were put to bed with fluids restricted until morning The second specimen was a 10 hour pooled urine from 8 p m to 6 a m for the Addis count Fluid restriction also made this specimen a mild concentration test Patients had breakfast in bed (one glass of juice or milk between 7 and 8 a m) and then took a lordotic position with pillows under the lumbar spine for two hour after which the third specimen was taken (Subsequent procedure eliminated the lordotic posture but the second recumbent specimen was retained as a check on the night collection) Patient was then permitted ward activity After lunch a fourth specimen was taken In some instances additional specimens were collected the next day after 30 minutes in exaggerated lordotic position standing or kneeling on a chair

Diagnostic criteria are summarized in Table 1 and incidence of each in Table 2 High incidence of benign inconstant albuminuria in young men is re emphasized At least 90% of all albuminuria cases fall in this group One variety of benign albuminuria is transitory and unpredictable in occurrence Emotional influences are major factors in its production by renal vasoconstriction Postural albuminuria accounts for the balance of the benign group Classification based purely on bodily position has little or no fundamental significance Lordosis is not the only postural influence causing albuminuria in this group the erect position and activity also are

(1) A Int M d 36 65 85 M r h 1952

in 0 4% sodium chloride solution with 1% of a fluid preparation of B complex vitamins

Under these conditions only those injected proteins having molecular weight of less than 70 000 were excreted Proteins prepared from the urine of patients classified as belonging to the group in which proteinuria occurs because of abnormalities in their plasma protein structure (prerenal proteinurias) were shown by this method to contain no appreciable amount of small protein molecules unless the urines from which they were derived contained Bence Jones protein Proteins prepared from urine of glomerular nephritis patients showed no appreciable amount of small protein molecules

II *Observations on urinary proteins*—Edward C Persike[8] determined the protein content of eight known protein preparations by the precipitate and biuret methods No direct relation between volume of packed precipitated protein and molecular weight was noted Each prepared protein produced a specific and different volume of protein precipitate under standard conditions Similar studies showed that urinary protein from a patient with prerenal proteinuria differed from that of four patients with renal proteinuria (degenerative stage of glomerular nephritis) forming a smaller volume of packed protein precipitate under standard conditions

III *Electrophoretic studies* were carried out by Eloise Jameson and T Addis[9] on the serum and urine of patients with prerenal proteinuria The serum and urine from one patient were observed both during an attack of unexplained proteinuria and during recovery The proteinuria was accompanied by changes in the serum chief of which was presence of a low gamma globulin and a split albumin Split beta and gamma globulins persisted during recovery long after the proteinuria had ceased and until the edema disappeared The preponderance of the urinary protein was homogeneous albumin In another patient edema persisted as long as the split fractions remained in either serum or urine Split albumins appeared in either serum or urine or both of each of several other patients The addition of gamma globulin to serum of one patient containing split albumin produced a homogeneous albumin The proportions of the proteins (excluding gamma

(9) A M A Arch I t M d 88 346 349 S pt mbe 1951
(9) Ib d pp 350 355

up of such patients is needed Clinical history often indicates slow tempo of progression especially in those due to latent glomerulonephritis and congenital renal defects Few were symptomatic or aware of any renal disease

Chronic glomerulonephritis was the least common renal disease More than half the patients were asymptomatic with no knowledge of previous renal disease Chronic pyelonephritis was slightly more frequent Diagnosis is often difficult since both albuminuria and pyuria may be intermittent The disease may be engrafted on congenital renal disorders Hypertension was observed in about one third of this group

Studies of Fluid, Electrolyte and Nitrogen Balance in Acute Renal Insufficiency Lloyd T Iseri Thomas M Batchelor Albert J Boyle and Gordon B Myers[2] (Detroit) studied 18 patients In five patients with severe acute renal insufficiency metabolic studies of sodium potassium chloride nitrogen and water balance were made for 6 23 days In 13 sodium and water balances were studied for longer periods

In one patient sulfonamide intoxication was the cause of the acute renal disease During the azotemic phase renal function tests showed low filtration fraction with initially normal maximal tubular excretion of para aminohippurate evidence of a primary glomerular lesion This was confirmed by renal biopsy (during convalescence) which showed diffuse glomerulitis and arteritis of the type ascribed to sulfonamide sensitization Hypertension developed as a late complication (after two months) and was accompanied by typical hypertensive renal functional changes namely increase in filtration fraction rise in glomerular filtration rate/maximal tubular excretion ratio to nearly normal and fall in renal blood flow/maximal tubular excretion ratio

Four patients had lower nephron nephrosis They showed three stages (1) shock for a few hours (2) oliguria for a few days to two weeks (3) diuresis for one to four weeks

Electrolyte changes during the oliguric stage consisted of hyponatremia and hypochloremia They were probably due to one or several of the following factors administration of water in excess of electrolyte intake movement of sodium into the cell shift of water from the cells to interstitial spaces renal loss of electrolytes and loss of electrolytes through

(2) A M A A h I t M d 89 188 15 F b ry 1952

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other channels There were two patients in whom fluid intake had been limited to 3 L daily severe water intoxication and pulmonary edema occurred in one peripheral edema in the other Hyperpotassemia in one of these was successfully treated by restriction of potassium intake increase in glycogen intake and intermittent gastric lavage In the others low protein high dextrose intake prevented hyperpotassemia and delayed rise in the blood nonprotein nitrogen level In the patients with lower nephron nephrosis this level fell as that of plasma sodium rose Urinary concentration of these changed reciprocally in two patients

During the diuretic stage plasma sodium and chloride levels fluctuated greatly Reduction in the plasma sodium and/or chloride level was especially striking at onset of diuresis Renal homeostasis was still impaired and had to be quickly and carefully corrected by regulating dietary intake of these electrolytes relative to water on the basis of plasma and urinary concentrations Intravenous administration of saline solution occasionally led to hyperchloremia apparently due to inability of the damaged renal tubules to reject this ion when in excess Even more striking was impairment of water reabsorption which resulted in dehydration

If detailed electrolyte determinations cannot be done the authors recommend administration of a sodium chloride solution of approximately half isotonic strength

Hypopotassemia was noted in three patients during the diuretic phase It was due to urinary loss (large urine volume with high potassium concentration) inadequate intake or failure of transfer to the extracellular compartment and losses through other channels Intake of at least 100 mEq potassium daily was necessary to maintain or restore normal plasma concentration

Low Potassium Syndrome Due to Defective Renal Tubular Mechanisms for Handling Potassium David P Earle Sol Sherry Ludwig E Eichna and Neal J Conan[3] (New York Univ) studied the mechanism of production of the low potassium syndrome in a Chinese man aged 42 with nephritis of unknown cause The syndrome consisted of intermittent bouts of muscular weakness atony of the bladder constipation and electrocardiographic changes of a broad flattened T wave

(3) Am. J Med 11 283 301 September 1951

prolonged Q T and P R intervals and dropped beats The plasma potassium level was 1 9 2 3 mEq/L when the patient was on a regular diet of 104 mEq/L potassium daily fell as low as 1 mEq/L on a potassium intake of 30 mEq/L daily and rarely exceeded 4 mEq/L when the potassium intake was 625 mEq/L Potassium balance was negative on an average potassium intake and became positive only when daily intake was increased to 425 mEq/L

Serum sodium levels were low and sodium balance negative except when sodium intake was high A reciprocal relation was seen between potassium and sodium balances when potassium intake was varied Plasma chloride level was low and chloride balance related to the sum of sodium and potassium balance

Potassium depletion affected muscle strength and vegetative nervous system although neither symptoms nor ECG changes were correlated to potassium level

Glomerular filtration rate renal plasma flow and maximal capacities of the renal tubules to excrete para aminohippurate and reabsorb glucose were one third normal Rate of glomerular filtration but not of the others varied directly with potassium intake During periods of low potassium intake and potassium plasma levels the kidneys continued to excrete large amounts of potassium This was not due to inability of the kidneys to defend by the usual mechanisms against either alkalosis or acidosis

With low potassium intake as much as 50 per cent of the potassium filtered at the glomerulus appeared in the urine (normal is less than 20 per cent) Tubular excretion of potassium was demonstrable when potassium intake was high Both decreased absorption and increased excretion of potassium were part of the renal tubular defect responsible for the excessive loss of potassium in the urine

Complications of Diuretic Phase of Lower Nephron Nephrosis Report of Case Manifesting Tetany Iver S Ravin Philip R Aronson and Jacob H Yules[4] (Boston City Hosp) point out that resumption of urine flow in lower nephron nephrosis usually augurs well for the ultimate outcome However during the diuretic phase of tubular recovery renal function may still be abnormal and electrolyte imbalance may

(4) New England J Med 244 830 832 May 1951

other channels There were two patients in whom fluid intake had been limited to 3 L daily severe water intoxication and pulmonary edema occurred in one, peripheral edema in the other Hyperpotassemia in one of these was successfully treated by restriction of potassium intake increase in glycogen intake and intermittent gastric lavage In the others low protein high dextrose intake prevented hyperpotassemia and delayed rise in the blood nonprotein nitrogen level In the patients with lower nephron nephrosis this level fell as that of plasma sodium rose Urinary concentration of these changed reciprocally in two patients

During the diuretic stage plasma sodium and chloride levels fluctuated greatly Reduction in the plasma sodium and/or chloride level was especially striking at onset of diuresis Renal homeostasis was still impaired and had to be quickly and carefully corrected by regulating dietary intake of these electrolytes relative to water on the basis of plasma and urinary concentrations Intravenous administration of saline solution occasionally led to hyperchloremia apparently due to inability of the damaged renal tubules to reject this ion when in excess Even more striking was impairment of water reabsorption which resulted in dehydration

If detailed electrolyte determinations cannot be done the authors recommend administration of a sodium chloride solution of approximately half isotonic strength

Hypopotassemia was noted in three patients during the diuretic phase It was due to urinary loss (large urine volume with high potassium concentration) inadequate intake or failure of transfer to the extracellular compartment and losses through other channels Intake of at least 100 mEq potassium daily was necessary to maintain or restore normal plasma concentration

Low Potassium Syndrome Due to Defective Renal Tubular Mechanisms for Handling Potassium David P Earle Sol Sherry Ludwig E Eichna and Neal J Conan[3] (New York Univ) studied the mechanism of production of the low potassium syndrome in a Chinese man aged 42 with nephritis of unknown cause The syndrome consisted of intermittent bouts of muscular weakness atony of the bladder constipation and electrocardiographic changes of a broad flattened T wave

(3) Am J Med 11 283 301 S pt mbe 1951

Girl aged 13 years 10 months with history of headaches for two years had blood pressure of 230/150 to 200/130 mm Hg mild hypertensive retinal changes Growth had been inhibited for two years height weight and development corresponded to that of a normal girl aged 10 or 11 The right kidney was small and renal function was reduced on that side Right nephrectomy revealed chronic pyelonephritis moderate hydronephrosis and patches of arteriosclerosis Blood pressure fell to 100/70 to 115/85 where it remained for the next two years Headaches disappeared she rapidly gained weight and height and the breasts countenance and body build became more mature

Changes in Serum Complement during Course and Treatment of Glomerulonephritis was studied by Kurt Lange Frank Graig Jacob Oberman Lawrence Slobody Gloria Ogur and Fred LoCasto[6] (New York Med College) by means of the complement binding sheep cell hemolytic system To obtain a high degree of sensitivity reading at 50% hemolysis was found imperative The dilution of the individual serum under investigation which just produced 50% hemolysis was noted and the complement content in units was calculated by dividing the dilution of the test serum by the dilution of standard complement needed to produce 50% hemolysis

On 68 subjects who were normal or had unrelated diseases 77 determinations were made The values varied between 1 0 3 0 units (average 1 68) Serum complement of normal persons is known to be fairly constant Of the 68 patients only 3 with cirrhosis of the liver and 1 just before death had low complement titers as compared with the controls Forty one determinations were made on 14 patients with acute glomerulonephritis in whom onset varied from 2 weeks to 20 months before the first examination All had a notable decrease of complement values ranging between 0 0 8 unit (average 0 32) When healing occurred the complement returned to normal It was usually still slightly depressed when all clinical and laboratory signs had subsided Often the normal range was reached within one week after complete clinical recovery All serums were inactivated and tested for anticomplementary properties in the usual way No serum was found to be anticomplementary The serum of one patient which contained no complement was mixed with that of a normal subject the complement activity remained the

(6) A M A A h I t Med 88 433 445 O tob 1951

be caused by the very measures designed to compensate for fluid and electrolyte loss during diuresis

Woman 36 was hospitalized after 12 hours of known anuria following self induced abortion three weeks before Diagnosis was lower nephron nephrosis or renal cortical necrosis She failed to urinate even on intravenous fluid therapy designed to supply calories counteract dehydration and achieve normal NaCl concentration Diuresis finally began after 13 days of oliguria (average daily urine flow 40 cc) amounting to 4 150 cc daily by the 23d day Acute pulmonary edema at this time was successfully treated but tetany followed with serum calcium content 4 8 mg and phosphorus 12 4 mg Intravenous infusion of calcium chloride parathyroid hormone and vitamin D with calcium lactate provided effective treatment

The following factors must be considered during the diuretic phase of recovery from lower nephron nephrosis (1) persistence of uremia (2) effects of massive diuresis (possible electrolyte and fluid depletion state) (3) effects of overtreatment (overburdening of cardiovascular system with excess fluids) (4) intercurrent disease (e g pulmonary and genitourinary infections) Thus although the patient was given only enough fluid to make up for loss in urine plus 1 000 cc for insensible and other losses pulmonary edema developed when over 4 000 cc fluid was given daily Alteration in calcium potassium ratio rather than the absolute value of each may have been at least partially responsible for tetany either ionized calcium depression or potassium elevation may cause it Thus in the presence of hypocalcemia and hypopotassemia potassium *and* calcium should be given The sequence of events leading to tetany in this case is thought to have been hypocalcemia and hyperphosphatemia during the renal shutdown (renal failure of phosphorus excretion with loss of calcium into intestine and urine) chronic acidosis with ionization of most of the serum calcium pulmonary edema with hyperventilation that increased serum pH and decreased ionized serum calcium values and potassium administration that changed the calcium potassium ratio which in turn caused tetany

Arterial Hypertension in Unilateral, Renal Disease with Inhibition of Growth Treated with Nephrectomy Haakon Storm Mathisen[5] (Oslo) reports a case believed similar to so called renal infantilism

(5) Act med sc d av 139 4 1 430 1951

atinine excretion but to a lesser extent thus causing a de creased clearance This is interpreted as due to tubular secre tion of exogenous creatinine Within two days after the sub jects were placed on a low meat diet urinary and serum creatinine concentrations showed no significant variations dur ing any 24 hour period Total urinary creatinine was not affected by a daily intake of 40 Gm protein (about 75 Gm meat)

The work of others indicates that tubular secretion of endogenous creatinine in renal disease is usually small enough not to interfere with the clinical usefulness of the endogenous creatinine clearance test

An average clearance of 137 L/24 hours was obtained with 32 determinations on 16 normal subjects (range 113 158 L/1 73 sg m body surface) Endogenous creatinine clearance was also determined 74 times on 22 patients with renal disease simultaneous 24 hour urea clearances were done with hourly tests on 10 of the patients By expressing creati nine clearance as per cent of normal for the subject s body surface area the data could be compared with urea clearances Comparable results were obtained

The 24 hour clearance test avoided many of the disad vantages of hourly tests minimizing temporary factors im proper timing and incomplete emptying and allowing normal activity Only one serum creatinine value was needed for each 24 hour test period

Serum creatinine concentration was less than 1 3 mg/100 cc in all normal subjects Some of the patients also had normal values whereas the 24 hour volumes determined by the creatinine method were definitely low When the serum creatinine level was more than 2 3 mg/100 cc filtrate volume was always less than 40% of normal When it rose to or above 5 mg corrected glomerular filtrate volume was always less than 20%

Amino Acid Metabolism in Cystinuria C E Dent and G A Rose[8] (Univ College Hosp London) studied 15 adults with cystinuria All were in good general health and all but two had had or were close relatives of patients with renal colic or stones The urine of each patient gave a strongly posi tive cyanide nitroprusside reaction Specimens were analyzed

(8) Q t. J Med 0 205 219 J ly 1951

same confirming the fact that the low titers were not due to the presence of anticomplement

In 13 cases clinically diagnosed as nephrosis 33 determinations were made The values obtained ranged between 0 09 1 3 unit (average 0 59) Although in general the values were not quite as low as those found in patients with acute glomerulonephritis they were definitely below normal

There was no trend to higher complement levels in nephrotic patients without clinical signs of glomerulonephritis when compared with those with such signs Six patients in uremia all with a distinct history of preceding glomerulonephritis were examined Two had uremia directly following acute glomerulonephritis and both had low complement values (0 0 04 unit) Both had rapid progression of the uremia with resultant death In the four others several years intervened between the attack of glomerulonephritis and onset of uremia All four had normal complement values and a slow progression of the uremia Ten patients with healed glomerulonephritis who had been previously under observation during their acute symptoms were subsequently followed at regular intervals for evidence of recurrences and signs of activity All patients showed normal complement levels and laboratory examination confirmed the absence of activity

Twenty Four Hourly Endogenous Creatinine Clearance as Clinical Measure of Functional State of Kidneys was evaluated by *Augusto A Camara Kenneth D Arn Ann Reimer* and *L H Newburgh*[7] (Univ of Michigan) They first tested the technic for determining serum creatinine With the Bonsnes and Taussky modification of the Folin method an average fasting creatinine concentration of 1 11 mg /100 cc (0 95 1 29 mg) was obtained on 11 normal young men Average for normal women was 0 86 mg /100 cc (0 77 0 98 mg) Best results were obtained with a 1 10 dilution of filtrate With lower dilution (1 4) more creatinine is absorbed by the protein precipitate

The level of fasting serum creatinine was found to bear no relation to different diets However after a meal containing meat there was a significant rise in serum creatinine Administration of carinamide to subjects on a high meat diet further increased serum creatinine concentration and also cre

(7) J Lab & Cl Med. 37 743 763 M y 1951

in the body tissues there is severe organic disease and death invariably occurs at an early age

Management of Glomerulonephritis is reviewed by H A Lindberg[9] (Northwestern Univ) Although about 90% of children recover completely from this disease only 60% of adults do Most of the others will progress to the subacute phase with death usually within a year or after a variable latent period chronic nephritis will develop with or without recurrences of acute nephritis The nephrotic syndrome may occur at any time during nephritis Treatment is most important during the early acute stage recurrent episode nephrotic stage and period of chronic nephritis with uremia

In acute nephritis which usually follows infection with hemolytic streptococci onset may be sudden with gross hematuria edema and hypertension or insidious with only minor symptom of fatigue Prophylaxis at this stage consists of vigorous treatment with antibiotics Removal of infectious foci after onset of acute nephritis may have no effect on its course Active treatment consists of bed rest low protein diet avoidance of excessive fluid intake and sodium intake restriction (200 500 mg daily) Bed rest is enforced during the inflammatory phase but when the character of the urinary sediment improves more activity is allowed Protein intake is increased to at least 1 Gm per kilogram of body weight daily once the acute phase has passed Acute hypertension and convulsions are treated with magnesium sulfate and barbiturates Oliguria is dealt with by limiting fluid intake (oral or intravenous intake of not more than 800 cc daily) and acidosis is treated with sodium bicarbonate or lactate solution Acute cardiac failure calls for rapid digitalization with or without aminophylline and oxygen by tent Use of ACTH and cortisone is contraindicated No treatment but frequent examinations are needed once acute nephritis has been overcome

The nephrotic syndrome is treated with a low sodium diet (1 Gm daily) and high protein intake (1 Gm/kg body weight daily in adults 1 5 Gm daily in children) to counteract loss of albumin in the urine and faulty protein metabolism both of which lead to hypoalbuminemia Intravenous administration of human albumin of low salt content (about 50 75

(9) CP 4 180 Sept mbe 19 1

for amino acids by paper chromatography Apart from the cystine a grossly excessive excretion of lysine was always found arginine was nearly always increased and fast arginine was found intermittently in one instance Cadaverine and putrescine were not detected The urine of a few patients was repeatedly examined at intervals for periods up to four years the pattern of excretion of amino acids although slightly different from patient to patient was fairly constant in any one patient and his affected relatives

The plasma of seven patients was analyzed for amino acid The concentration of all detectable amino acids was normal except in one patient whose plasma sometimes contained an abnormal concentration of fast arginine Cystine concentration in two patients was also found to be normal when determined by microbiologic assay

The immediate cause of the grossly excessive excretion of cystine lysine and arginine in the urine is a low renal threshold presumably due to a defective capacity of the renal tubules to reabsorb these substances The three amino acids may be handled in the same way by the tubule owing to their general structural resemblance to each other but there is no metabolic relation between them There was no evidence of any error in amino acid metabolism in the body tissues except for the renal tubules in the cases of cystinuria

Diseases such as Fanconi s syndrome and hepatolenticular degeneration in which there is excessive excretion of cystine in the urine show what is described as gross amino aciduria an excessive excretion of nearly all the common acidic neutral and basic amino acids These diseases are easily distinguishable by paper chromatographic analysis of the urine

Diagnosis of cystinuria should be limited to cases present from birth and characterized by excretion in the urine of large quantities of cystine (about 1 Gm in 24 hours in the adult) lysine and usually arginine The condition often present in the patient s relatives may result in formation of stones composed almo t entirely of cystine Except for the possibility of kidney damage from stone formation the patients are in good health In some excretion of cystine is intermediate between the normal and cystinuric levels

There is no etiologic relation between cystinuria and the condition known as cystinosis In the latter cystine is deposited

$NaHCO_3$ 0 1 Gm calcium gluconate and 20 Gm glucose (3 500 cc over seven hours)

In man a total of 28 22 mEq potassium is secreted in 24 hours above the ligament of Treitz except for that secreted in the saliva compared to the 13 5 mEq secreted in 24 hours for the rest of the intestinal tract From this the stomach and duodenum would be expected to be far more efficient than any other section of the intestinal tract in the dialysis of potassium However results in the dog and unpublished data in man showed the stomach and duodenum to be relatively inefficient When the mucous membrane of the stomach and duodenum come in contact with the perfusate solution the cells of these organs do not act as a dialyzing or secreting membrane for potassium as readily as do those of the jejunum This certainly seems to be the case regarding the jejunum in the dog and experiments in man confirmed this Efficiency of the stomach duodenum and jejunum increased greatly in that order The data also indicated that potassium comes across the membrane of stomach duodenum and jejunum more readily when there is an excess in the plasma and extracellular fluids Comparison of lavage of the normal jejunum with that of the jejunum in an animal with hyperpotassemia showed that it was possible to extract about three times the amount of potassium when total renal insufficiency and hyperpotassemia were present The results in animals cannot always be completely translated into the physiology of man but the data obtained tended to substantiate the feasibility of controlling hyperpotassemia and intoxication by intestinal lavage

In two patients with hyperpotassemia perfusion of the jejunum through a Miller Abbott tube and Wangensteen suction caused precipitous fall of potassium to normal levels It is necessary in clinical cases to follow the plasma potassium every two hours because in one patient its blood concentration was reduced to 2 5 mEq /L and characteristic changes of hypopotassemia appeared in the electrocardiogram Lavage of the upper intestine is just as efficacious as the artificial kidney or any other method for removal of electrolytes or urea When compared to the artificial kidney it is not so rapid but far less complex and essentially without hazards

Gm daily) may be necessary to increase temporarily plasma osmotic pressure and thus decrease edema Gelatin preparations given intravenously have occasionally been effective and are cheaper They do not seem to be toxic when given for a short period in a dose of 50 Gm daily Mineral diuretics may also be used and powdered urea is often effective (45 90 Gm daily as tolerated followed by orange juice) but mercurials must be given cautiously and never intravenously Nephrotic crisis in children is treated with 10% solution of protein hydrolysate intravenously and with antibiotics

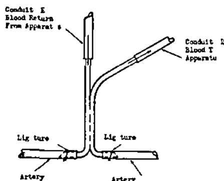
Chronic nephritis in the uremic stage calls for a low protein (0 5 Gm /kg body weight daily) and a high fluid intake (3-4 L) to maintain good urine output Anemia is best treated with frequent small transfusions of whole blood or packed red cells Electrolyte imbalance is corrected as necessary Diarrhea often seen because the bowel excretes some ammonia and urea is treated by the usual methods and by changing intestinal bacterial flora with acidophilus milk Sodium chloride intake may have to be restricted Fluids may be given parenterally both to improve urine output and correct acidosis or alkalosis Caloric value can be increased by adding 20% glucose Symptomatic treatment with sedatives and gastric lavages for nausea and vomiting are helpful Although the disease is always fatal vigorous treatment can make life more tolerable and postpone death

Acute Renal Insufficiency and Role of Potassium with Treatment by Intestinal Lavage Therapy in acute uremia with anuria or severe oliguria must include a consideration of electrolyte imbalance and especially potassium concentrations in the body fluids Electrolyte imbalance may play a more significant role in acute uremia than has been thought in the past Indeed the retention of urea and possibly other nitrogenous products is easily reduced with intestinal lavage whereas dangerous levels of potassium may be more difficult to handle Robert A Kelley and Lucius D Hill III[1] (Univ of Virginia) studied the lavage of this electrolyte by perfusing the stomach duodenum and jejunum of dogs which were normal or had acute renal insufficiency and hyperpotassemia with a solution containing in each liter 6 Gm NaCl 3 Gm

(1) J U ol 66 645 660 No mbe 1951

distal stump of the radial artery or to a suitable vein Artery to artery instead of artery to vein flow may eliminate the adverse *effect of the arteriovenous shunt of the latter method at high flow* rates Figure 79 shows a convenient method for obtaining artery to artery flow by use of a double passage cannula

The dialyzing tubing with its circulating rinsing fluid may occupy part or nearly the whole volume of the chamber Since the volume of blood in the chamber is controlled a large dialyzing surface can be exposed with a minimum of blood (10 50 ml) In tubular blood flow in other systems



F g 79 —Art ry-to- pp t to- t y blood fl w w th se f gl d ble- p k 1 (Cou t y f G J R d G L J S 115 285 88 M 14 1952)

only the layer of blood at the periphery of the tube in contact with the dialyzing membrane is dialyzed blood not at the periphery is surplus Furthermore the blood flow at the periphery of the tube is slowest

Artificial Kidney Paul E Teschan and Marion E Mc Dowell[3] (M C U S N) discuss its clinical uses They used the Kolff artificial kidney as modified by Merrill Hemo dialysis was carried on at the rate of 200 300 ml /minute the dialysate of 100 L containing 660 Gm sodium chloride 225 Gm sodium bicarbonate 30 Gm potassium chloride 22 Gm magnesium chloride 40 Gm calcium chloride and 200 Gm glucose Potassium chloride concentration was varied as indicated by certain circumstances such as potassium in toxication Dialysis was usually continued for six hours

(3) U S A med F M J 3 391 399 M h 195

Artificial Kidney A Simplified Apparatus which is small safe and efficient and easily used in small hospitals and clinics as routine treatment is described by John R Guarino and Louis J Guarino (Cambridge Mass)

APPARATUS (Fig 78) —This consists of a silicone coated glass chamber with detachable upper portion Incorporated in the chamber in concentric layers is 23 ft of ¾ in cellophane tubing with free ends connected to a reservoir containing rinsing fluid The fluid leaves the reservoir through conduit A is pumped through conduit B into the cellophane tubing in the chamber and leaves

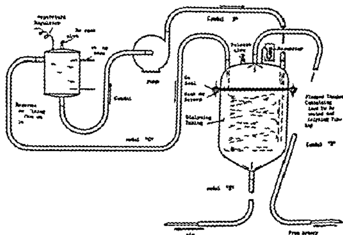


Fig 78 —Artificial kidney Diameter of chamber 4 in Length 7 Length of dialyzing tubing 23 ft diameter ¾ in dialyzing surface area 4113 sq cm. Volume of blood in chamber 50 ml (Courtesy of Guarino J R and Guarino L J Science 115 285 88 Mar 14 1952)

the chamber through conduit C to return to the reservoir providing a continuous flow of rinsing fluid through the cellophane tubing Circulation through the cellophane tubing has been maintained without difficulty at rates up to 300 ml/min A mixture of oxygen and carbon dioxide may enter the reservoir to control pH of fluid.

As the arterial blood enters the chamber an air cushion is formed above the blood surface The air cushion and air vent control volume or level of blood in the chamber Hydrostatic pressure of the perfusion or rinsing fluid is maintained equal to or above that of the blood The blood is allowed to flow over the cellophane tubing in a nondirectional flow forming in effect a blood shower Treated blood leaves the chamber through conduit E and is returned to the subject through a cannula inserted into the

(2) Science 115 285 8 Mar 14 1952

two patients and recovery was complete in one with lower nephron nephrosis due to transfusion after uterine hemorrhage

Up to 197 Gm urea was removed in the bath during a single dialysis period with a corresponding drop in the blood urea nitrogen value Other chemical changes were lowered serum potassium concentration and return toward normal of other electrolytes and metabolites When desired rapid de hydration could also be achieved 2 2½% hypertonic glucose solution was placed in the dialysate and small doses of insulin were given at the same time to keep the blood glucose level low and thus increase the blood bath gradient As much as 4 kg body weight (presumably of fluid) was lost in a single six hour dialysis period

The authors stress use of other measures such as correc tion of anemia adequate nutrition and avoidance of over hydration before and in addition to application of the arti ficial kidney They suggest that the artificial kidney be used in acute renal failure when hyperpotassemia or overhydration is present and oliguria has persisted for over six days It may also be useful preoperatively in chronic uremia due to surgically correctible conditions

Treatment of Uremia Use and Indications for High Caloric Low Protein Diet, Dialyzing Methods and Replace ment Transfusion W J Kolff[5] believes that regardless of the cause of acute anuric uremia and chronic uremia treatment should be guided by the following principles

1 Maintenance (or re toration) of body fluid and elec trolyte balance Daily intake should not exceed 750 cc fluid in addition to replacement of fluid lost by vomiting or diarrhea Blood CO_2 combining power and sodium chloride and po tassium levels should be determined frequently as a guide to administration of electrolytes Moderate decrease in sodium chloride concentration may be advantageous since it reduces blood pressure and diminishes risk of convulsions and con gestive heart failure High caloric intake controls acidosis in part If the CO_2 combining power falls below 25 vol % sodium bicarbonate may be given Calcium gluconate or chloride is used to correct low calcium levels and aluminum hydroxide has been recommended for hyperphosphatemia

2 Suppression of protein metabolism This is accomplished

(5) Cl l d Cl Q t 18 145 158 J ly 1951

Heparin (150 mg every six hours) served as the anti coagulant

Use of this method was followed by striking improvement in chemical balance of the blood in potassium intoxication ECG s were made since they are a more accurate index of actual or potential myocardial abnormalities than determina tions of serum potassium concentration In three patients with acute renal insufficiency (glomerulonephritis with anuria hemoglobinuric nephrosis with anuria potassium intoxica tion with oliguria) there were dramatic changes in urea nitrogen sodium potassium and chloride levels after dialysis Recovery was complete in two (nephrosis and potassium in toxication)

Other indications for hemodialysis include barbiturate intoxication salicylism oliguria and/or hypotension of severe hepatic failure hepatic coma without oliguria or hypotension exacerbation of chronic uremia and as a preoperative measure in chronic uremia due to prostatic obstruction Bleeding from any source is the only absolute contraindication to use of hemodialysis

Clinical Use of Artificial Kidney F John Lewis Milton P Reiser Richard H Egdahl Francisco L Raffucci and Edmund B Flink[4] (Minneapolis) used the Kolff apparatus as modified by Merrill 26 times in 15 patients They changed the entire bath twice in each six hour period of dialysis Heparin (180 220 mg during dialysis) was used as an anti coagulant Clinical changes noted during dialysis consisted of increased drowsiness followed by alertness and feeling of well being at the end of the dialysis period Occasionally systolic blood pressure temporarily increased 40 mm or more Hg with little change in diastolic pressure or heart rate

Six patients had lower nephron nephrosis two acute renal failure due to glomerulonephritis five various types of chronic renal disease one cirrhosis with cancer of the liver and one encephalitis with diabetic coma In most immediate results were good but the ultimate outcome was not changed in patients with chronic renal disease or those in the terminal stages of acute renal failure In the patient with polycystic disease of the kidney and liver death was postponed for four months Preoperative dialysis allowed successful surgery in

(4) J al La t 72 1 7 J nuary 195

restore the hemoglobin content Exchange transfusion attempted in one instance caused panmyelophthisis in the donor and has therefore been abandoned

By paying attention to restriction of fluid intake and correction of electrolyte imbalance giving a high caloric low protein diet and if necessary adding one of the dialyzing methods acute uremia may be overcome and chronic uremia be at least partially counteracted The patient will be made more comfortable and duration of life significantly prolonged

[With such a sodium chloride free solution for dialysis frequent analyses of the blood for sodium and chloride are obviously necessary In addition, the patient should be observed carefully for the clinical signs of decreased osmolar concentration Such manifestations include headaches vomiting and in severe instances convulsions The decision as to what type of dialyzing fluid to utilize has to be based on the combination of sound clinical judgment and frequently repeated analyses —Ed]

Probable Clinical Utility of Cation Exchange Resins is reviewed by L Greenman J H Peters F M Mateer and T S Danowski[6] (Univ of Pittsburgh) The resin may serve in some borderline situations even without dietary restriction to tilt the balance of sodium enough to prevent further retention Thus some patients may be maintained on full diet with resin added whereas others may only need partial limitation of exogenous sodium These exchangers usually remove 1 mEq sodium or less/Gm of resin ingested when the diet contains sodium potassium excretion/Gm resin is usually about 50% greater If essentially complete sodium restriction is achieved only small increments of this cation will be removed in the stool As ordinary full diets provide an intake of 100 300 mEq sodium in the course of 24 hours these agents alone in amounts up to 60 Gm day cannot produce negative balances as a result of stool losses A larger intake of resin might shift the sodium balance to negative but prescriptions in such dosage too often prove burdensome

Effects of hydrogen and ammonium cycle resins are not limited to deviation of sodium to stools Both produce an acidosis which in edema control can be viewed as desirable in subjects with unimpaired renal function Frank acidosis and overbreathing may accompany ingestion of acidifying resins especially in patients with far advanced renal failure It is doubtful that accenting a definite acidosis—the result of renal insufficiency—in any way stimulates urinary sodium

(6) J Cl I e t 30 1027 1031 Sept mbe 1951

by a high caloric low protein diet which can reduce urea excretion to as little as 2 5 Gm /24 hours The diet can be given as a mixture of butter and sugar if oral feeding is possible as the fat emulsion lipomul® oral via a stomach tube or in desperately ill patients as a slow continuous drip of 40% glucose through a small plastic cardiac catheter with its tip in the right auricle Such catheters have been left in place as long as 20 days

3 Prevention or treatment of infection Antibiotics such as penicillin or aureomycin are indicated but use of sulfonamides should be avoided

4 Removal of substances normally excreted by kidney If the procedures previously described are used early and thoroughly diuresis usually occurs However, if these measures are not observed or if there is excessive protein breakdown artificial dialyzing may be necessary The artificial kidney has been used successfully in acute and occasionally chronic uremia for bridging over the anuric period, correcting electrolyte balance relieving edema and adding large amounts of glucose to the body

Indications for peritoneal lavage are the same as those for use of the artificial kidney Although the procedure is mechanically simpler than the artificial kidney, it is less easily controlled and may cause peritonitis It can be very effective especially for immediate brief application if other methods are not at once available or feasible Kolff has used it by putting small tubes into the peritoneum through trocars and perfusing at the rate of 1 L/hour from a tank containing 28 L of electrolytically balanced fluid antibiotics and heparin

Dialysis through an isolated loop of small intestine (about 2 m) has also proved effective especially if long term treatment is necessary for chronic uremia A suggested dialyzing fluid contains NaCl 0 $NaHCO_3$ 200 KCl 40 $CaCl_2$ 28 sucrose 6 000 and glucose 3 600 mg/100 ml Sucrose is added to make the fluid hypertonic and increase caloric intake

Replacement transfusion has also been tried A large amount of blood is removed from an arm vein and discarded while an equal amount of blood is introduced simultaneously through another vein Since several liters are needed every other day to remove sufficient urea it is a costly procedure However such transfusions—on a small scale—are useful to

desired Attempts to maintain daily intake of resin at 30-40 Gm (amounts readily taken by essentially healthy children) were only partially successful Mean daily intake was only 17 7 ± 12 4 Gm Patients on an unrestricted diet tolerated resin far better and in larger amounts than those on the milk formula

Serum carbon dioxide content decreased on the average 4 10 mEq/L below control values and returned to previous levels after cessation of therapy This was not accompanied by a rise in mean serum chloride The only other measured serum constituent to show change was potassium Average levels diminished by almost 1 mEq during therapy and subsequently returned to pretreatment values Stool sodium did not rise significantly during resin treatment All four patients continued to deliver their edema with only occasional interruptions whether they were receiving resin or not Mean balance values during pre and postresin periods clearly indicated that the low sodium regimen may by itself have induced negative external balances of sodium and chloride with decrease in extracellular volume diuresis and loss of body weight Rates of extracellular sodium and water loss and of decrease in body weight characteristic of control periods on low sodium therapy only were not visibly accelerated by these amounts of resin Patients were in positive nitrogen balance during control and resin periods thus losses in body weight cannot be attributed to inadequate intake

In two patients the low sodium regimen was replaced during continued resin ingestion by a full diet containing ordinary amounts of sodium In each instance the patients ate well and took larger amounts of resin The daily stool sodium and potassium output exceeded values observed in control subjects on comparable diets without resin and greatly exceeded those in the same patients while on resin and low sodium diet Chloride and nitrogen output were not unusual

Resin can increase stool losses of sodium and potassium during periods when the diet contains ample amounts of sodium

Studies of Cation Exchange Resins Their Optimal Potassium Content for Clinical Use Resins are known to reduce absorption of sodium and potassium and to a much smaller

and water losses it is therefore judicious to identify such patients and treat them either with lesser amounts of resin or with nonacidifying resins in other cycles Whether increase in stool potassium losses and production of negative potassium balances are desirable or not depends on the patient Starvation mercurial diuretics or even ACTH or cortisone will increase potassium requirements On the other hand in patients with excessive body stores of potassium this effect would be beneficial Sodium cycle resin is not generally useful though it might be most useful in a specific situation Accumulation of potassium accompanies sodium excess in most renal disease states

Experience with the calcium cycle resin is limited Gram for gram it should prove less effective in inducing diuresis in the absence of acidifying effect In renal failure this attribute may make it useful if it serves to increase sodium and potassium losses in stools The calcium released could conceivably be precipitated with phosphate in the intestinal lumen this may be useful in modifying the hyperphosphatemia of renal failure and (directly or indirectly) the hypocalcemia However calcium elution in favor of sodium or of potassium is inefficient The possibility that use of milk formulas because of relatively high calcium content may make other resins less efficient since hydrogen ammonium and potassium resins will tend to take up calcium rather than sodium especially if sodium concentration in the medium is minimal as in sodium free milk

Sodium Restriction and Cation Exchange Resin Therapy in Nephrotic Children was studied by F M Mateer Loraine H Erhard Marjorie Price F A Weigand J H Peters T S Danowski R Tarail and L Greenman[7] (Univ of Pittsburgh) A carboxylic cation exchange resin in the hydrogen cycle was administered during 15 periods of three to six days to four edematous nephrotic children With few exceptions sodium intake was restricted to 1 3 mEq/day before during and after resin administration Diet consisted of a low sodium milk with added milk protein and carbohydrate and contained adequate calories and nitrogen and considerable amounts of chloride and potassium Water was allowed as

(7) J Cl n I k 30 1018 1026 S pt mber 1951

directly affects water reabsorption by the renal tubule cells and intact renal tubular function is indispensable for urines of maximum concentration The patient need not be prepared Kai Bjerre Christensen[9] (Copenhagen) compared the concentration (Addis Shevky) test and the pitressin® test

METHOD—In the Addis Shevky test fluid is restricted for 24 hours and urine from the last 12 hours is collected for calculation of specific gravity

In the Pitressin® test a preparation containing 20 pressor units/ml and 5% oxytocin is used it is feasible at any time without preparation of the patient After the patient has voided as completely as possible 0 5 ml pitressin® is injected intramuscularly One two and three hours after injection separate urine specimens are again collected

In 93 normal patients average maximum specific gravity by the Addis Shevky test was 1 031 and by the pitressin® test 1 030 with a common standard deviation of ± 0 0035 In 27 patients with impaired renal function average specific gravity by both tests was 1 021 with standard deviations of ± 0 0039 and ± 0 0034 Differences with the two tests in individual patients were generally small Mechanisms for the two tests do not differ fundamentally With chronic non nephrogenous generalized edema repeated pitressin® tests gave significantly higher values The clinical impression was that the pitressin® test results will always be higher and less equivocal in edematous patients but statistical significance of these results was difficult to establish Secondary effects of the pitressin® test were slight and transitory The test is *inadvisable for patients with acute or severe coronary insufficiency* Hypersensitivity to posterior pituitary extract is extremely rare

Studies on Renal Hyperlipemia Alvar Svanborg[1] (Karolinska Hosp Stockholm) studied rapidly progressing hyperlipemia after bilateral ligation of the ureters in rabbits Administration of renal venous blood or tissue extract from normal kidney did not appear to affect this hyperlipemia contrary to earlier results which suggested that the kidney normally secretes a lipid metabolism regulating hormone The role of the kidney in the breakdown of lipids was therefore investigated Rapid passage of the blood through the kidney and synthesis of lipids in the kidney prevent determination

(9) Act m d sc d 142 215 230 1952
(1) Ib d l 141 pp 264 1951

degree of calcium Usually, 0 8 1 2 mEq sodium and 0 4-0 8 mEq potassium are bound per Gm resin Usual clinical dose of resin is 50 Gm daily

Evan W McChesney[8] (Rensselaer N Y) determined the optimal potassium content of resins to prevent potassium deficiency which is the most frequent clinical complication of their use In vitro experiments showed that when tested against phosphate buffer solutions of pH 6 4 several sulfonic type resins had available capacities of 3 4 mEq/Gm Their affinity for potassium was about 50 times that for sodium Carboxylic type resins had an available capacity of 2 3 mEq/Gm At an acidity found in gastric juice alkali salts of sulfonic type resins were fairly stable but alkali salts of carboxylic type resins were hydrolyzed markedly decreasing gastric acidity

For both types of resins in the K form optimal potassium content was 1 2 mEq /Gm at this level fecal loss of sodium and potassium is about canceled by the potassium taken with the resin and loss of fixed base is thus decreased If some acidosis is desired potassium content should be nearer 1 mEq /Gm With adequate potassium balance sodium combining power is essentially unchanged

In vivo studies on rats extrapolated to man indicate that daily intake of 12 5 Gm potassium form and 37 5 Gm NH_4 form carboxylic resin (a total of 90 mEq K) can bind about 1 Gm sodium in the intestine while maintaining a positive potassium balance and causing little change in acid base balance At the same time it would neutralize about 4 L gastric juice of normal acidity The same combination of sulfonic resin (containing 52 mEq K) can bind 1 3 Gm sodium in the intestine while maintaining a positive potassium balance but causing a small net alkali loss It would neutralize about 1 600 cc gastric juice of normal acidity

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(8) J Lab & Clin Med 38 199 09 Aug 1951

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(8) J Lab & Clin Med 38 199 09 Aug 1951

grayish or pinkish scars the pelves were scarred and tips of the pyramids flattened The heart was uniformly hypertrophied Histologic studies revealed severe diffuse chronic pyelonephritis in 43 of the 50 acute pyelonephritis in 3 a combination of slight to moderate diffuse pyelonephritis with arteriosclerosis and arteriolosclerosis in 3 and only arteriosclerosis and arteriolar sclerosis in 1

These findings indicate that chronic pyelonephritis is the primary lesion in most cases of malignant hypertension Microscopic lesions are characteristic Severe changes in interstitial tissue and tubular apparatus as against minimal glomerular damage are constantly observed Severe vascular changes are uniformly present particularly arteritis deformans Interstitial inflammation extends to the intrarenal vasculature first producing acute lesions which resemble panarteritis and then scarring with narrowed deformed arterial lumens The last stage resembles arteriosclerosis microscopically but the process is really an arteritis deformans The narrowing which is anatomically profound in the interlobular vessels causes a more severe ischemia than that in chronic glomerulonephritis or arterial or arteriolar nephrosclerosis This may account for the proportionately higher arterial tension in chronic pyelonephritis than in other chronic kidney diseases Arteriosclerosis is probably secondary to prolonged and severe hypertension or may be the end result of an inflammatory arteriolitis similar to the deforming endarteritis of larger intrarenal vessels Arteriolonecrosis is often sparse and is obviously a terminal or preterminal sign because there is no significant reaction to necrosis or hemorrhage It is a result rather than a cause of uremia

These lesions constitute a variety of pyelonephritis which is probably a clinical as well as an anatomic entity There is usually no history of urinary infection or obstruction A history of pyelonephritis in pregnancy or of definite pyelonephritis attack is rare The disease has an insidious onset and is unrecognizable until symptoms of essential hypertension appear often culminating in rapid renal failure Acute exacerbation of pyelonephritis was found in 50% this apparently is the common precipitating factor for uremia The authors suggest that malignant hypertension and malignant nephrosclerosis are vague nonetiologic terms that describe

of kidney function in the breakdown of lipids by means of lipid concentration analyses in afferent and efferent renal blood

A special homogenizer was used to study enzymatic activity of fragmented cell suspensions Lipase (tributyrinase) and phosphomonoesterase activity were studied in serum and in kidney and liver tissue suspensions from normal and ligated rabbits Normal kidney suspensions showed the same over all triglyceride splitting capacity as did liver tissue Lipase and alkaline phosphomonoesterase activity decreased considerably in kidney tissue concurrently with a hyperlipemia in animals with ureters ligated bilaterally comparable decrease in enzyme activity could not be shown in serum and liver suspensions In both kidney and liver suspensions the acid phosphomonoesterase activity remained the same indicating that the drop in enzyme activity in the kidney after ureteral ligation is not general Lipase activities of the same order of magnitude were shown in the kidney and liver tissue in man

Whereas mass of liver tis ue exceeds that of kidney tissue volume of blood passing through the kidneys exceeds that through the liver the kidney is probably significant in the breakdown of lipids Possibly hyperlipemia after nephrectomy or bilateral ureteral ligation depends on a decrease in normal lipid splitting function of the kidney It seems reasonable that the lipase activity of the kidney is principally in cells of the tubules and not in endothelium of the glomeruli Accordingly hyperlipemia would occur in nephritis and nephrosis when those cells of the tubules in which there normally is a strong lipase activity are affected

Pyelonephritis Lenta Otto Saphir and Bernard Taylor[2] (Michael Reese Hosp) studied the kidneys at 50 autopsies on patients with hypertension complicated by uremia (malignant hypertension) and compared them with 50 on persons with essential hypertension complicated by vascular accident or heart failure Analysis of clinical features showed that the uremic patients were generally younger more hypertensive had constant anemia frequent albuminuria and inconstant urinary findings Uremic kidneys were considerably smaller than the controls the cortex was shallow yellowish with

( ) An I t Med 36 1017 1041 Ap 1 1952

of renal lesion the disease in rats simulates the nephrotic syndrome of infants and children The same experimental procedure produces the disease in rats in its pure or mixed form

no consistent morphologic entity and should therefore be discarded further that diffuse chronic pyelonephritis of this type be referred to as pyelonephritis lenta to distinguish it from the destructive variety of pyelonephritis

Nephrotic Syndrome in Rats Chronic renal disease in rats especially in the Long Evans strain induced by antikidney serum simulates the nephrotic syndrome in children Walter Heymann and Herbert Z Lund[3] (Western Reserve Univ) produced chronic renal disease in 235 rats 4-5 weeks old of the Long Evans strain by intravenous injection of nephrotoxic serums Antiserums against rat kidneys were prepared by injecting suspensions of perfused rat kidneys into rabbits Massive proteinuria largely without hematuria was promptly noted Severe edema and ascites were noted in 35% of animals in the first two to three weeks

Within the first two weeks 32% died The disease was spontaneously cured in 30% and chronic renal disease sometimes lasting as long as 13 months was found in the others Of 125 sick rats 74% remained normotensive Fluctuating and moderately severe hypertension was noted in the others The blood was clearly hypoproteinemic and hyperlipemic in the earliest phase slowly subsiding as the disease progressed but never attaining normal values while the disease persisted With a few exceptions creatinine concentration remained normal in all phases Azotemia was frequently pronounced in severe disease at onset It subsided regularly within the first two months and about 50% of rats had slight azotemia in the late stages

Histologic analyses led to the following conclusions (1) Nephrotoxin produces primarily a degenerative lesion with changes in glomeruli and tubules (2) there may be recovery from the degenerative phase or it may be followed at different intervals by a variable degree of fibrous proliferation in the glomerular tufts and capsules Whether this fibrosis of glomeruli is direct repair of damaged glomeruli or a result of abnormal glomerular function could not be determined (3) in the degenerative phase the lesion produces the nephrotic syndrome In the proliferative phase depending on degree hypertension and uremia are found In symptoms and course in deviation of blood chemistry and in morphology

(3) P d t cs 7 691 706 May 1951

The Digestive System



GEORGE B EUSTERMAN M.D

THE DIGESTIVE SYSTEM



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PART V

THE DIGESTIVE SYSTEM

THE ESOPHAGUS STOMACH AND DUODENUM

Esophageal Sensitivity to Mecholyl* in Cardiospasm and various other conditions was studied by Philip Kramer and Franz J Ingelfinger[1] (Boston) A Miller Abbott tube with a balloon capacity of 50 cc was placed in the lower third of the esophagus inflated against a pressure of 20 25 cm water and connected to a kymograph After a control tracing of 10 30 minutes each subject was given 1 10 mg mecholyl* intramuscularly In addition barium swallows were observed fluoroscopically

In 18 subjects without esophageal disease mecholyl* did not alter the basal motility pattern strikingly though generally tone and phasic activity were moderately increased In each of 11 patients with practically all possible degrees of cardiospasm mecholyl* produced a tetanic contraction which expelled all air from the balloon The contraction could also be seen fluoroscopically after a barium swallow (Figs 80 and 81) Six mg of mecholyl* is probably the optimal dose to achieve results with minimal side effects Symptoms after injection resembled those after a meal but were more severe

Three patients with esophageal spasm showed the same response as normal subjects In four patients with esophageal stricture and one with polypoid carcinoma mecholyl* produced a moderate increase in tone and contractions but not so pronounced as in cardiospasm Balloon kymograph records of four patients with scleroderma showed markedly decreased tone and minimal phasic activity with but a negligible increase after administration of mecholyl*

In addition to providing a possible diagnostic tool response of the esophagus to mecholyl* supports the concept that cardiospasm is a neuromuscular disorder involving not

(1) G t oe t 1 gy 19 242 251 O tobe 1951

only the cardia but also the lower esophagus Its three major attributes suggested by the authors are (1) tapered narrowing in distal 2 4 cm of esophagus during and after swallowing (2) abnormal peristaltic activity and impaired propulsion with variable decrease in tone in lower one third to two



Fg 80 (l ft) — E ph g f p t nt w th d p
Fg 81 (gl) — S m e th m n t tt adm t at o f 6 mg mech lyl t m l ly
(C t y f K m P d I g lfi g F J G st t l gy 19 4? 251 O t b 1951)

thirds of esophagus and (3) hypersensitivity of lower one third to two thirds of esophagus to parasympathomimetic agents

Treatment of Cardiospasm Analysis of Twelve Year Experience Cardiospasm is a nonorganic stenosis of the lower esophagus The portion involved is at and immediately above the juncture of the esophagus and stomach and is seldom more than 4 6 cm long (Fig 82) Present treatment is directed at relief of obstruction Exact diagnosis is important Cardiospasm may be differentiated from diffuse spasm of the esophagus which does not respond favorably to dilatation or surgical treatment by passage of an olive tipped bougie (41 F) over a previously swallowed thread In cardiospasm the ob

struction is localized to a short segment of esophagus at the cardia whereas in diffuse spasm obstruction begins in the midesophagus and extends all the way to the stomach

Arthur M Ol en Stuart W Harrington Herman J Moersch and Howard A Andersen reviewed cases of 601 pa tients treated by dilatation at the Mayo Clinic in 1935-47 in 46 by passage of sounds alone in 555 by hydrostatic dilatation

TECHNIC—Dilatations are carried out over a previously swal lowed twisted thread of EL buttonhole silk Patient starts to



F g 8 —C d p m A mod t d l ta n B d ffu d l t t o C p o ou d d l t t gul t n d elo gat (C te y f Olsen A M et al J Th S g 164 187 A gu t 1951)

swallow the thread 24 hours in advance slowly swallowing about 1 ft every hour up to 15 ft Once the thread is firmly anchored preliminary dilatation with metal sounds are performed The patient sits in a low chair facing the physician A 41 F olive tipped metal bougie is attached to the end of a flexible whalebone staff and passed over the thread into the stomach A second dilatation follows immediately u ing a 50 or 60 F Plummer sound guided over the thread by a flexible wire spiral The patient then rests for 48-72 hours Preliminary dilatation with sounds is important diagno tically and facilitat s sub equent hydrostatic dilatation by relieving esophageal retention The hydrostatic dilator is pas ed over the previ ously swallowed thread to insure safety of the procedure and proper placement of the bag in the cardia Before the dilator is passed a 41 F olive is pa sed into the stomach The exact distance from the point of obstruction to the upper incisor teeth is determined and marked off on the tube of the hydrostatic dilator Once in place the

(2) J Th c S g 22 164 187 Aug t 1951

bag is carefully inflated to 22 24 ft (9 5 10 3 lb /sq in) of water pressure and the pressure maintained for several seconds The patient will usually have great pain if the bag is properly placed This pain subsides rapidly after the dilator is withdrawn One evidence of a successful dilatation is a small amount of fresh blood on the distal end of the dilator If relief from dysphagia is not complete the patient again swallows a thread and a second hydrostatic dilatation is performed 48 or 72 hours after the first More than two or three hydrostatic dilatations are seldom necessary and the entire treatment program is usually completed in 7 10 days

Relief from dysphagia for 4 16 years was obtained from a single course of dilatation in 272 (60 2%) of 452 traced cases In the other 180 dysphagia recurred in less than four years Of these patients 94 returned for a second course 36 (38 3%) were relieved of dysphagia for four years or more Of the 58 patients who obtained unsatisfactory results from the second course of treatment 26 returned one or more times only 5 (19 2%) were satisfactorily relieved by additional hydrostatic dilatations Adding all courses of treatment 313 (69 2%) of the 452 traced patients obtained relief for four years or more Had it been possible to re treat all patients who had unsatisfactory results after the first course the total number of satisfactory results would have been 341 (75 4%) for two courses or 362 (80 1%) for all courses About 20% of patients cannot be permanently relieved by dilatation Moreover if satisfactory results are not obtained after two courses additional dilatation is not likely to succeed

Conditions associated with less favorable results were slight or pronounced enlargement of the esophagus pain as a prominent symptom and coexisting pulsion diverticula or hiatus hernia Complications after hydrostatic dilatation included rupture of the esophageal wall near the cardia in 10 patients aspiration pneumonitis in 6 and hematemesis in 7 Two patients died of mediastinitis after esophageal rupture a mortality of 0 56% Both deaths occurred during the first year before the advent of antibiotics and before radical surgery was considered feasible

Surgery should be considered for patients not responding to two or three courses of dilatation During the study 23 patients were operated on usually for the foregoing indication Results were best in cases in which there were only moderate secondary changes of dilatation and thickening of the esophageal wall Results were poorest when dilatation pro

nounced especially when it was associated with retention and elongation of the esophagus regardless of type of operative procedure Operative procedures included transgastric retrograde dilatation and/or sympathectomy esophagogastrostomy (Heyrovsky or Grondahl) cardioplasty (Wendel) trans thoracic resection of cardia and lower esophagus with esophagogastric anastomosis and extramucous esophagocardiomyotomy (Heller) Transgastric retrograde dilatation and/or sympathectomy almost always gave unsatisfactory results (poor in five cases good in one) These procedures are no longer used Results obtained with the other five types of operation although varied were essentially the same excepting probably esophagocardiomyotomy The immediate and early result was almost always satisfactory and the patient was greatly relieved because of removal of obstruction In six however the long term result was unsatisfactory because of esophagitis from free regurgitation of gastric secretions into the esophagus In three cases with fair results the esophagitis was less severe The Heller operation is apparently the most advantageous since it permits the cardia to retain some of its sphincteric property thereby reducing the danger of peptic esophagitis and ulceration If this procedure is not feasible and one is performed which destroys the sphincteric action of the cardia an effort should be made to reduce the acid production of the stomach

Duodenal Distention as Cause of Epigastric Pain was studied by Pekka Brummer and Ilmari Ruikka[3] (Oulu Finland) in 30 test subjects 14 of whom had symptoms of gastric dyspepsia and particularly of epigastric pain None had organic gastric disease as shown by roentgen examination In the control series of 14 persons none had gastric dyspepsia but most had functional or organic disorders which suggested that the general pain threshold was lowered Two other persons who could not be classified definitely in either category made up a borderline group The first portion of the duodenum was intubated under x ray observation with a double lumen Miller Abbott tube one lumen of which was connected to a balloon The balloon was inflated to 80-100 ml unless pain was felt earlier

In 11 of the 14 patients with dyspepsia distention produced

(3) Acta med. Scandinav. 141 95 99 1951

distinct pain in a circumscribed area in the epigastrium which in several instances resembled that ordinarily felt by the patients Four controls felt definite and one indefinite pain In the borderline group no pain was felt during the test These findings point to a lowered duodenal pain threshold in patients with gastric dyspepsia Since this is probably true of gastric pain threshold as well it suggests that various stimuli ordinarily not noticed such as gastric and duodenal motility disturbances may cause distress in patients with gastric dyspepsia

Gastrographic Investigations of Normal and Pathologic Motility of Stomach J P Doret[4] (University of Geneva) carried out an exhaustive gastrographic investigation concerning the motive power which regulates gastric motility namely the propulsive peristalsis and the inhibiting one of the Hirsch von Mering reflex The threshold of this reflex which controls the passage of food through the pylorus into the duodenum and the intensity of the propulsive force vary from person to person

Variations in the reflex threshold during the various stages of digestion provided explanations of the cause of error in interpretation of the Kay test This test is based on the fact that when a normal person drinks a small amount of water during gastric motor activity while fasting gastric contractions cease for a variable period Since the same phenomenon does not always occur in patients with ulcers Kay believed the test could be used for diagnosis of duodenal ulcers especially The reflex threshold rises as the duodenum receives and neutralizes gastric juice with higher concentrations of free hydrochloric acid variation of threshold also occurs in response to various foods In patients with the same degree of gastric acidity delay in evacuation is proportional to the fat concentration in the stomach With equal fat concentrations delay is more pronounced in patients with achlorhydria Stimulation of the duodenum by water in the Kay test is subject to the same law This shows why inhibition of the reflex is usual in normal persons and patients with chronic hyperchlorhydric gastritis variable in patients with gastric ulcer and finally absent most of the time in patients with duodenal ulcer with its well known tendency to hyperchlorhydria The Kay test

may indicate hyperchlorhydria with gastric hypermotility but these conditions although they occur most often in duodenal ulcer are also symptoms of gastric ulcer and pseudo ulcerous dyspeptic syndromes consequently the test lacks diagnostic value The functional disturbance revealed by it however is probably a factor in ulcer pathogenesis

Gastrography was used to study the physiopathology of gastroduodenal pain especially the epigastric cramps of ulcer patients and dyspeptics The divergence in opinions held by many authorities arises from failure to discriminate between constant pain and intermittent cramps and from a misunderstanding of the functional relation between acid secretion and motility of the stomach Three points however are generally accepted (1) similarity of the painful cramps whatever the cause whether organic or functional (2) prime importance of gastric hypersensibility in the genesis of the pain and (3) existence of intermittent cramps synchronous with gastric contractions The stimuli capable of causing spontaneous gastric pain are primarily motor i e normal contractions of the stomach pylorus or duodenum and to a higher degree spasmodic contractions or distention of the gastric wall Hydrochloric acid may also influence production of pain either directly or by lowering pain threshold through its hyperemic effect Intermittent sensations called hunger pangs are caused by tonic stomach contractions these are usually silent but may enter the field of consciousness when pain threshold has been lowered by hyperemia accompanying a work period It *is only a step from hunger pangs to intermittent epigastric* cramps Pains of this type may be felt at two moments in gastric activity during a period of work with fasting and at the end of evacuation of a meal Whether intermittent pain occurs during fasting or in the postprandial period its appearance seems to depend on the presence of a small amount of liquid in the stomach on which the gastric contractions may exert pressure If the gastric contents cannot pass through the pylorus tonic contractions will raise the intragastric pressure more than they otherwise would thus increasing the likelihood of pain That the muscle contractions may be painful in themselves is shown by the fact that healthy persons may experience hunger pains Both contractions and pain may be stopped by various methods complete evacuation of the

stomach ingestion of food etc Different results are obtained depending on the height of the *duodenal reflex* threshold degree of acidity of gastric contents and concentration of acid or alkaline solutions introduced into the stomach Sodium bi carbonate will sometimes increase the contractions making them more painful whereas augmenting the level of free acid by ingestion of a solution of hydrochloric acid may bring them to a halt Acidity thus plays a secondary part in genesis of hunger pains With continuous pain however hyper chlorhydria has an important effect on its appearance In creased gastroduodenal sensitivity is apparently chiefly re sponsible for continuous postprandial pain whether the free hydrochloric acid acts directly or indirectly on the sensitive organ has not yet been clearly shown In persons with a low reflex threshold however excess acidity stimulates the reflex so intensely that the contractions become spasmodic and pain ful Measures which combat the inhibitive reflex relax the pyloroduodenal spasm excite gastric contractions and restart gastric evacuation stop the pain The efficacy of hot applica tions which relieve postprandial pain by relaxing the pyloric spasm and exciting gastric contractions (dermovisceral re flex) furnishes additional proof of the importance of motor factors in continuous pain of this kind

[Proponents of the motor factor in the mechanisms of gastroduodenal pain will find much comfort in the results of this investigation On the other hand the contribution of Palmer and his collaborators and of Bonney and Pickering (1947 YEAR BOOK p 650) that the chemical factor is the all important one in the genesis of pain in uncomplicated ulcer has the support of many clinicians and surgeons It is to be noted that the results of their investigations and those of others supporting the chemical theory were given due consideration and challenged by Doret Even though conceding the paramount importance of the chemical factor in ulcer we are all aware of the frequent painful phenomena which arise in the digestive tube often closely simulating the pain pattern of ulcer in the complete absence of any pathologic changes Such can best be ex plained on the basis of Doret s observations It is reasonable to assume that the interaction of both chemical and motility factors is operative under certain circumstances —Ed]

Achylia Gastrica Keystone in Development and Eradica tion of Macrocytic Achylic Anemia (Pernicious Anemia, Ad dison Biermer) Contrary to popular opinion achylia gastrica and achlorhydria are not synonymous Achlorhydria is lack of free hydrochloric acid a symptom found secondarily in many diseases and conditions and without clinical significance Achylia gastrica is complete absence of gastric juice primary

and constitutional leading to pernicious anemia Three strictly circumscribed signs characterize this entity (1) absolute lack of gastric juice with lack of all constituents of gastric secretion (2) disturbance of chymification and (3) disturbance of motility These signs can be determined only by the Boas Ewald test meal The alcohol test with histamine injection shows only presence or absence of hydrochloric acid and is therefore inadequate for differential diagnosis between achylia gastrica and achlorhydria Those who consider achylia gastrica achlorhydria and anacidity an identical condition because of lack of free hydrochloric acid state that its cause is gastritis with inflammatory and atrophic changes This has been disproved by Frederick S Weinberg[5] (New York City) who found no gastritis in the stomachs of 11 patients with achylia gastrica who died of pernicious anemia The changes noted were atrophic rather than inflammatory and were limited to the fundus and cardia in three patients there was no change in the gastric mucosa which was normal

Achlorhydria in cancer tuberculosis and other diseases can be observed in its origin There is a gradual progressive diminution of free hydrochloric acid which parallels the progressive severity of the disease The condition therefore is found in only a certain per cent of the cases and may be reversible However achylia gastrica is present in all cases of pernicious anemia and is never progressive it is present not only at onset of the disease but before Thus it should be possible to demonstrate development of pernicious anemia and to make an early diagnosis by systematic blood examinations in cases of achylia gastrica Such examinations often show hemoglobin and erythrocyte values above normal In many cases so called normal blood has been found but there were changes which permitted diagnosis of latent or early pernicious anemia These include macrocytosis with color index above 1 lymphocytosis leukopenia with hypersegmentation diminished monocytes and diminished platelets

Achylia gastrica has been detected in newborn infants and in children and is accompanied by the same blood changes as in adults hypo and hyperchromic anemias There is a familial occurrence of the disease it is inborn and hereditary Wherever there is a family tree with achylia gastrica there is

(5) A J D g t D 18 351 362 Dec mb 1951

a mixed occurrence of achylia gastrica and pernicious anemia The task is to find these cases of achylia gastrica This can be done by having a certain institution in a given district collect the names of all patients with pernicious anemia and then search the whole genealogic tree of the patients with all its collaterals A gastric analysis and blood examination must be performed on each of the relatives Those with achylia gastrica are potential pernicious anemia patients as long as they live and must be under steady observation They may be treated in two ways (1) by examinations at regular intervals to find out how many show blood and nerve changes in the course of time and the rate of development and (2) by use of liver or other helpful substances to prevent development of pernicious anemia

Weinberg suggests that the name pernicious anemia is now misleading because the disease is no longer pernicious There fore since it belongs in the group of macrocytic anemias and is preceded by achylia gastrica it should be called macro cytic achylic anemia

[The author assembles much convincing evidence to support his con tentions The lack of all the constituents of gastric secretion one of the three characteristics of achylia gastrica would presuppose the absence of Castle s intrinsic hemopoietic factor According to Glass and Boyd (Gastroenterology 20 452 1952) evidence has been recently adduced for the intimate relation of glandular mucoprotein a product of the mucoid cells of the neck of gastric glands located chiefly in the fundus and corpus of the stomach to Castle s factor At any rate it is apparent that we should be more circumspect in terminology our foreign colleagues seem more derelict in this respect One should differentiate between achylia gastrica and achlorhydria and whether the latter is true or false The blanket term achylia should be dropped—Ed]

Why Do a Gastric Analysis? J L A Roth and H L Bockus[6] (Univ of Pennsylvania) point out that the acidity of gastric contents is the net result of (1) the total volume and rate of parietal secretion reflecting the interplay of stimu lating and inhibiting mechanisms and (2) evacuation or alter tion of parietal secretion

The fractional gastric analysis of Rehfuss with some form of carbohydrate as a test meal is the commonest procedure for clinical study of gastric function It provides a crude but com plete measure of the stomach s work not only its secretory capacity but also its motor functions Examination of the fast ing gastric residuum may supply useful information Recov

(6) Gastroenterology 18 546 565 Aug st 1951

ery of gross food from the stomach after a 12 hour fast is almost always due to delay in stomach emptying and often to obstruction at or near the pylorus If free acid is present but no bile or food particles a fasting volume in excess of 50 cc suggests hypersecretion

Normally the odor of gastric contents is pungent and penetrating but it is important to recognize the odor due to a reflux of colonic content for this may be the first indication of a gastrojejunocolic fistula A similar odor may be detected in advanced ulcerative and necrotic carcinoma of the stomach If the fluid in the fasting residuum is colored by gross blood then carcinoma ulcer or severe erosive gastritis should be suspected and the tube removed Microscopic examination of the fasting residuum may reveal parasites tubercle bacilli cholesterol crystals and calcium bilirubinate pigment or malignant cells in tissue fragments

After complete evacuation of the fasting residuum postprandial samples should be aspirated every 15 minutes for at least 2 hours The stomach may exhibit average acidity after a carbohydrate meal but show a hyperacid response to alcohol or meat extract meals so that a normal and a hypersecretory stomach cannot be differentiated If an initial hyperacidity is found after the Ewald meal histamine injection will produce little if any increase in free acid concentration Starches are not secretogogues The stimulating action of these test meals is due to psychic secretion and distention with the release of gastrin The magnitude of the response is probably conditioned by the level of the vagus activity In a patient with duodenal ulcer the level of acidity in response to the Ewald meal in a fractional gastric analysis may serve as a guide in therapy or prognosis Partial neutralization of gastric contents is all that needs to be achieved by the strictest medical regimen The need for antacids and atropine is indicated in the higher grades of hyperacidity Complicated ulcer is associated with high grade hyperacidity oftener than is uncomplicated ulcer Probably the more profound the hyperacidity the greater the chance of development of a gastrojejunal ulcer after partial gastric resection On this basis more extensive resection complementary vagotomy or stricter postoperative management may be indicated

If no free acid is found in fractional gastric analysis with

a mixed occurrence of achylia gastrica and pernicious anemia The task is to find these cases of achylia gastrica This can be done by having a certain institution in a given district collect the names of all patients with pernicious anemia and then search the whole genealogic tree of the patients with all its collaterals A gastric analysis and blood examination must be performed on each of the relatives Those with achylia gastrica are potential pernicious anemia patients as long as they live and must be under steady observation They may be treated in two ways (1) by examinations at regular intervals to find out how many show blood and nerve changes in the course of time and the rate of development and (2) by use of liver or other helpful substances to prevent development of pernicious anemia

Weinberg suggests that the name pernicious anemia is now misleading because the disease is no longer pernicious There fore since it belongs in the group of macrocytic anemias and is preceded by achylia gastrica it should be called macro cytic achylic anemia

[The author assembles much convincing evidence to support his con tentions The lack of all the constituents of gastric secretion, one of the three characteristics of achylia gastrica would presuppose the absence of Castle s intrinsic hemopoietic factor According to Glass and Boyd (Gastroenterology 20 452 1952) evidence has been recently adduced for the intimate relation of glandular mucoprotein a product of the mucoid cells of the neck of gastric glands located chiefly in the fundus and corpus of the stomach to Castle s factor At any rate it is apparent that we should be more circumspect in terminology our foreign colleagues seem more derelict in this respect One should differentiate between achylia gastrica and achlorhydria and whether the latter is true or false. The blanket term achylia should be dropped —Ed]

Why Do a Gastric Analysis? J L A Roth and H L. Bockus[6] (Univ of Pennsylvania) point out that the acidity of gastric contents is the net result of (1) the total volume and rate of parietal secretion reflecting the interplay of stimu lating and inhibiting mechanisms and (2) evacuation or alter tion of parietal secretion

The fractional gastric analysis of Rehfuss with some form of carbohydrate as a test meal is the commonest procedure for clinical study of gastric function It provides a crude but com plete measure of the stomach s work not only its secretory capacity but also its motor functions Examination of the fast ing gastric residuum may supply useful information Recov

technic and interpretation of the insulin test for vagal gastric secretion are of added timely and instructive interest —Ed]

Twenty four Hour Gastric Analysis in Patients with Histamine Achlorhydria, as described by James and Pickering was used by G Watkinson and A H James in the study of 22 patients Results cast doubt on the reliability of histamine meals in assessment of achlorhydria even when repeated on

ACHLORHYDRIA AND PEPTIC ULCER IN 12 PATIENTS

A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	C mm
(4	R G	+	O	2	2 6	4	
50	R G	+	O	2	1 7	18	
5?	R G	+	O	2	1 7	13	
50	R G	+	O	2	1 4	6	
6–	R G	+	H	–	1 5	9	
56	R —	+	H	2	1 4	11	
57	R —	+	H	1	1 6	7	
50	R —	—	H	4	1 5	18	*Duodenal ulcer 5 yr before*
8	R G	—	H	7	1 4	18	Gastric ulcer on 3 occasions in ?0 yr
37	R —	+	H	3	? ?	14	
48	R —	+	H	1	3 5	—	Subsequent acid secretion on repeated hi tamine stimulation
40	R —	+	O	1	4 6	—	
Mean					21	9.8	

R d log d mo t t on f I r t
C g t osc p m pe t ed
O onfi m d by pe n d b t logy
H c firm d by ncompl t d b l g w th m d cal t eatm t

several occasions Among 10 patients with micro or macro cytic anemia acidity never exceeded pH 4 2 which suggested that all had true achlorhydria Achlorhydria was associated with peptic ulcer in 12 patients in 10 of whom the 24 hour test showed that pH 3 0 was not exceeded for periods of 4-18 hours (table)

This evidence indicates that the Rehfuss histamine meal overestimates the incidence of achlorhydria particularly in cases associated with peptic ulcer It was concluded that large chronic gastric ulcers may develop in patients in whom the gastric contents are acid only for short periods during the day

[Inve t gations in recent years have c clu ively shown that estab-

(7) Cl Sc 10 55 66 M y 19 1

an Ewald test meal the procedure should be repeated with histamine before true achlorhydria is diagnosed The potency of the histamine preparation should be determined by use on other patients to make certain that the particular lot is not inactive or has not lost potency by deterioration Adequacy of the dose of histamine base is inferred from recognizable physiologic effects such as facial flush headache or slight fall in blood pressure since the threshold dose for producing these effects is greater than that for stimulating the parietal cells The maximal dose tolerated without untoward effects should be used 0 1 mg histamine base or 0 275 mg histamine acid phosphate/10 kg body weight is a satisfactory empiric dose for this purpose Fractional sampling of gastric contents every 15 minutes should be continued for a minimum of 2 hours to detect the slight and transient appearance of hydrochloric acid and any delayed response Demonstration of true achlorhydria provides crucial information when diagnosis concerns primary pernicious anemia stomach carcinoma and a pseudoulcer syndrome or invalidates a postvagotomy negative insulin test

The insulin test has a limited use in evaluating the completeness of vagotomy and its reliability in prognosis of clinical results remains to be demonstrated The sustained gastric secretory response to caffeine may aid in diagnosis of duodenal ulcer disease The caffeine gastric analysis may be used to greatest advantage (1) when the patient has a characteristic ulcer history but careful x ray studies do not demonstrate a crater or deformity of duodenal cap or (2) when the patient presents the differential diagnosis of asymptomatic upper intestinal bleeding with negative x ray examination of the esophagus stomach duodenum or small intestine

[This informative contribution contains much food for thought for those who would dispense with gastric analysis altogether More reasonable is the attitude of those who resort to gastric analysis only if the roentgenologic examination is inconclusive and further information is desired The authors properly advocate the fractional method even though it is more time consuming and requires trained personnel This procedure or the alcohol test meal undoubtedly will supplant the traditional Ewald test eventually Though physiologists who use the dye dilution technic point out certain shortcomings of the routine methods in vogue the latter are sufficiently informative from a practical clinical standpoint.

The author s observations on the steps necessary to establish the presence of a true achlorhydria and the several possibilities for error in

[The diagnostic significance of volume and acid concentration of the morning basal secretion after a 12 hour fast has been the subject of much investigation in the past decade. Results reported here are in accord with the well established fact that gastric secretory re ponse to various timuli is usually greater in patients with duodenal ulcer than in normal persons whereas re ponse in patients with ga tric ulcer is either the same or fre quently lower than normal

A comparable investigation by Grandjean (Acta. med. scandinav 143 6 1952) showed that almost 37% of ulcer patients had normal values for the amount and acidity of fasting secretion however gastric, duodenal and stomal ulcers were considered together In duodenal ulcers there was a fairly high inciden e of hypersecretion He concluded that examination of fasting secretion is of value only for demonstration of achlorhydria and that diagnosis is based primarily on anamnesis radiologic and possibly gastroscopic findings blood sedimentation rate and presence or absence of occult melena —Ed]

Clinical Evaluation of Caffeine Gastric Analysis in Duodenal Ulcer Patients Caffeine directly stimulates the parietal cell and also potentiates gastric secretory response to other stimuli such as hist mine alcohol cholinergic drugs electric stimulation of the vagi and meat extractives Acid output induced by caffeine plus histamine is greater than the sum of responses to these stimuli singly The mechanism is not understood but recent evidence suggests that caffeine acts as a catalyst to the intracellular enzyme systems involved in hydrochloric acid formation

To appraise frequency of qualitative difference between ulcer and nonulcer patients and to establish a quantitative criterion for sustained stimulation in response to caffeine James L A Roth[9] (Univ of Pennsylvania) performed fractional gastric analyses with caffeine test meal on 344 persons 182 of whom had histories and x ray confirmation of active recurrent duodenal ulcer disease The control group of 162 patients had miscellaneous (other than duodenal ulcer) or no demonstrable disease None of the controls had achlorhydria and all had normal upper gastrointestinal x ray studies except those with gastritis duodenitis benign gastric ulcer or carcinoma of the stomach

TECHNIC —After removal of the fasting residuum and after basal secretion had been obtained for 30 minutes the test meal of 500 mg caffeine odium benzoate (equivalent to 250 mg caffeine alkaloid) in 200 cc water was given by Levin tube then removed in 30 minutes The stomach was emptied every 10 minutes thereafter for an additional 90 minutes This procedure was used on 100 duodenal ulcer patients and 100 controls (group A) The technic was then modified

(9) G t oe t logy 19 199 215 Octobe 1951

lishing a definitive diagnosis of true achlorhydria is not as easy as was formerly believed Investigators have overcome one objection of physiologists by having subjects eat a regular meal the natural stimulus to gastric secretion As a result of earlier research of this nature, some discerning clinicians have resorted to aspiration four hours after a heavy meal This usually reveals adequate or high acid concentration when Ewald type test meals had only disclosed achlorhydria.—Ed.]

Simple Measure of Gastric Secretion in Man Comparison of 1 Hour Basal Secretion, Histamine Secretion and 12 Hour Nocturnal Gastric Secretion Erwin Levin Joseph B Kirsner and Walter L Palmer[8] (Univ of Chicago) describe a simple and reliable procedure for characterizing quantitatively the gastric secretory response in man This method obviates use of various time consuming test meals which require special personnel and may like the histamine test produce undesirable side effects or like the fasting 12 hour nocturnal gastric secretion test be impractical for routine use

Data on the one hour morning basal secretion and histamine response were obtained for 560 normal persons (319 male) 222 duodenal ulcer patients (174 male) and 50 patients (40 male) with benign gastric ulcer Fasting gastric secretion was measured at 15 minute intervals for 1 hour (8 30-9 30 a m) and compared with secretion for 1 hour after administration of 0 01 mg histamine base/kg body weight and continuous 12 hour night secretion (8 30 p m to 8 30 a m)

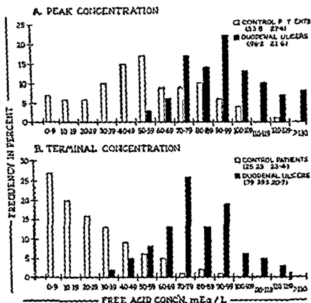
The data demonstrate that the procedure using morning basal secretion parallels the other two whenever there is acid in the basal secretion and that this analysis may yield information of diagnostic value In every instance average basal secretion was significantly higher in patients with duodenal ulcer and lowest in patients with gastric ulcer These differences were maintained in comparisons by age and sex

Simple measure of the fractionated one hour morning basal secretion yields the information on secretory response of the stomach necessary for routine clinical purposes As with other secretory tests diagnostic value is modified whenever acid is present throughout the period although average secretion of the three groups differs significantly However when one or more periods show no acid active duodenal ulcer is unlikely The only practical indication for administration of histamine caffeine or alcohol is in individual cases in which true achlorhydria must be established

(8) Gastroenterology 19 88 98 September 1951

results whereas if a terminal concentration of 50 mEq./L. is taken as upper normal 14% false positive results are obtained In duodenal ulcer patients 5% false negative results would appear with outputs less than 225 mg hydrochloric acid/90 minutes and 7% false negative results with terminal concentrations less than 50 mEq /L

Group A was also tested with the Ewald meal Although



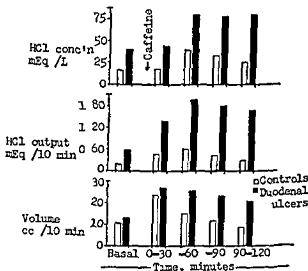
F g 84 —F eq n y d t b t sh w ng i p n peak d te m nal f ee d t n ponse t aft t t meal P nthet l figur p e se t me) ±) ta d d d t n (Co t y f R th J L A G t e ente logy 19 199 215 O t be 1951)

the mean maximal acidity of duodenal ulcer patients in response to the carbohydrate test meal was significantly higher than in the control group the values overlapped so closely that response to the Ewald meal had little diagnostic value

Differences between mean peak concentrations and mean terminal concentrations of free acid in response to caffeine (Fig 84) were also significant statistically (p values < 0 01)

for 82 other patients and 62 new controls (group B) by testing basal secretion every 15 minutes until free acid concentration was stable instilling the test meal for 30 minutes and collecting 10 cc samples of gastric contents every 15 minutes for 120 minutes after the meal Topfer s reagent and phenolphthalein were used as indicators for free (pH 3 5) and total (pH 8 5) acid in the titrations

Since most of the water in gastric juice is secreted by the parietal cell the acid concentration of mixed gastric juice varies directly with the volume rate of parietal secretion



F g 83—S ta d l m o tput d co centr t n of f e a d in p t ts w th duod nal ul r d s (Cou te y of Roth J L A G troe ter logy 19 199 215 O tobe 1951)

Figure 83 shows results for group A Data are averaged for half hour periods to simplify analysis and the average during the last half hour of the two hour gastric analysis represents the terminal free acid concentration Sustained increase in concentration as well as volume and output of free acid was found

The superiority of the criterion of concentration over output as an index of sustained response is apparent from the false positive and negative results obtained with the same data in group A If an output of 225 mg /90 minutes is the upper limit of normal 29% of control patients show false positive

sin In each instance corticotrophin increased acid secretion to active duodenal ulcer level (Fig 86) Cortisone will induce similar gastric response Maximal acid and pepsin effects were noted after 7 14 days of continuous therapy This coincides with average duration of corticotrophin or cortisone therapy which precedes reactivation perforation or hemorrhage from peptic ulcer Uropepsin excretion in normal per ons receiving corticotrophin also increased to levels commonly observed in

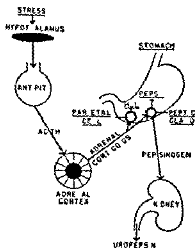


Fig 85 — H m l p hw y wh by mot on l nd phy l m y ffect th l m h ult g n sed p du n f g byd hl d d pep n. (C t y f G y S J et l J A M A 147 15 9 1537 D 15 1951)

patients with active duodenal ulcer The mean uropepsin increase was 194% compared to an average rise of 182% in pepsin concentration Unusually high uropepsin levels were observed in a patient who died of massive gastric hemorrhage and duodenal perforation after four courses of corticotrophin therapy for rheumatoid arthritis

Corticotrophin in 100 mg doses daily produced in a patient with active gastric ulcer definite evidence of impending perforation with localized peritonitis and severe aggravation of ulcer symptoms gastric acidity tripled and gastric pepsin and urinary uropepsin secretion rose noticeably When cortico

Sustained free acid response to caffeine was observed in (1) patients in anxiety tensional states with excess vagus activity (2) patients with prepyloric ulcers, (3) preulcer individuals and (4) most duodenal ulcer patients If the conditioning influence of the vagus is responsible for response to caffeine extreme caution must be used in diagnosis or prognosis in an individual who shows only excess vagus activity (high basal secretion rapid gastrointestinal motility)

Within limits of false positive and negative results the caffeine analysis may aid diagnosis when (*a*) the patient has a characteristic history but careful x ray studies fail to reveal a duodenal cap deformity or (*b*) when differential diagnosis of asymptomatic upper gastrointestinal bleeding must be made and other studies fail to reveal the cause

Chronic Stress and Peptic Ulcer I Effect of Corticotrophin (ACTH) and Cortisone on Gastric Secretion. Importance of stress factors in the pathogenesis and chronicity of gastroduodenal ulcers has been established and peptic ulcer has often been designated as a stress disease Acute gastric and duodenal hyperemia and erosions sometimes with hemorrhage are characteristic of the first stage of the general adaptation syndrome Chronic stress fear and anxiety or hostility and resentment are all associated with increased hydrochloric acid secretion Continuous administration of corticotrophin simulates chronic stress and results in increased gastric acidity and gastric pepsin with subsequent peptic ulceration perforation or hemorrhage according to Seymour J Cray John A Benson Jr Robert W Reifenstein and Howard M Spiro[1] (Boston) Moreover because of emotional or systemic stress the hypothalamus appears to secrete a humoral substance which stimulates the pituitary gland to secrete corticotrophin Corticotrophin in turn activates the adrenal cortex to release a number of steroid hormones including cortisone and cortisone like compounds which then cause the gastric glands to secrete acid and pepsin (Fig 85)

Corticotrophin given intramuscularly to six normal subjects in doses of 100-160 mg daily for three to four weeks produced a decided increase approximating 200% in basal and nocturnal gastric secretion of hydrochloric acid and pep-

(1) J A M A 147 1529 1537 Dec 15 1951

secretion is of utmost importance in choosing between vagotomy and partial gastrectomy To help solve this problem Ove Noring[2] (Copenhagen) conducted sham feeding tests on 38 ulcer patients before and 11 14 days after partial Billroth II gastrectomy Tests showed pronounced reduction in all components of the gastric juice volume of secretion acidity and total chloride content Changes in pepsin values were not statistically significant Reduction was not a transitory phenomenon because a study of 38 patients 2 36 months after operation showed further reduction in cephalic secretion Thirteen patients were tested at all three periods

Although the risk of wrong positioning of the tube is greater after resection with concomitant false achlorhydria if it drops into the jejunum injection and aspiration of air through the tube become much easier as the tip passes the cardia making the position in this study fairly certain without x ray control Postoperative gastric changes might influence secretion but this does not explain the reduction as secretion must be presumed to have been reproduced within 11 14 days or at least within 2 36 months Inflammatory changes of postoperative gastritis do not set in until several years after operation Moreover postoperative gastritis and acidity are not believed to be related Thus reduction in cephalic secretion 11 14 days after resection is apparently not traceable to changes in gastric cells

Biliary admixture after operation appeared to influence only the lowest acidities in the group but could not explain the considerable reduction in acidity found in the experiments These findings are in accord with those in the literature

To avoid altered general condition as a source of error patients were not tested until their general condition was restored to normal To learn whether experimental conditions were the same before and after operation histamine tests were made in 12 cases before and after resection because of the direct effect of histamine on the cells The average depression in volume of secretion was the same in sham feeding as in histamine stimulation while the acidity was reduced far more in the former

It is concluded that surgery removes a link in the process eliciting cephalic gastric secretion This secretion therefore

( ) G t oe t logy 19 118 125 S pt mbe 1951

trophin was discontinued the patient became asymptomatic and pepsin and uropepsin values returned to pretreatment levels

Another patient with healed inactive duodenal ulcer secreted 5 550 mg free HCl during corticotrophin therapy an unprecedented level for active duodenal ulcer The 12 hour nocturnal gastric juice volume also rose to a level far above the average recorded in active duodenal ulcer patients Active duodenal ulcer developed in this patient two months later

It is concluded that prolonged administration of corticotrophin or cortisone may subsequently become hazardous to

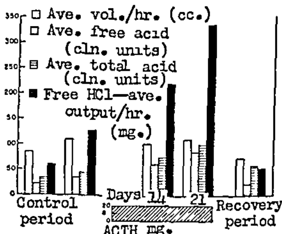


Fig 86—Eff t f c t t ph n ga t c ty (b s l cc t on) n e p tie t h w g a e f e hydro hl c e d d ing adm t t (C t y of C ay S J t l J A M A 147 1529 1537 De 15 1951)

peptic ulcer patients X ray examination of the stomach and use of such antacids as aluminum hydroxide before hormone treatment are indicated for such patients Similar precautions are recommended in hormone treatment of patients with anoxia and intracranial lesions for whom corticotrophin and cortisone constitute additional stress factors

Cephalic Phase of Gastric Secretion Following Partial Gastrectomy Although complete vagotomy is known to abolish cephalic gastric secretion it has generally been assumed that this phase of secretion is unaffected by resection of the pylorus and antrum Influence of the pyloric region on vagal

achlorhydria If long term studies confirm this it would offer promise of fewer operative failures

[These findings confirm previous studies at the same hospital Post operative achlorhydria is almost unfailing insurance against recurrent ulceration It is highly probable that adequate resection for duodenal ulcer plus bilateral vagotomy would minimize the number of postoperative ulcers This may eventually prove justifiable as a routine procedure in the younger patient with hypersecretory highly acid chemism if operation is imperative —Ed]

Physiology of Gastric Secretion and Its Relation to the Ulcer Problem are discussed by Lester R Dragstedt Harry A Oberhelman Jr and Edward R Woodward[4] (Univ of Chicago) In normal animals the nervous phase of gastric secretion accounts for about 45% of the gastric juice secreted in 24 hours the gastric phase about 45% and the intestinal phase 10% or less The nervous or cephalic phase is medi ated by the vagus nerves and is permanently abolished by complete vagotomy The gastric phase is mediated by the mucous membrane of the antrum of the stomach which func tions as an endocrine organ for manufacture of the gastric secretory stimulant gastrin Removal of the antrum in Pavlov pouch dogs or transplantation to the abdominal wall so that it does not come in contact with food abolishes the gastric phase When both the nervous and the gastric phases are eliminated by vagotomy and antrum resection the secretion of acid by the body and fundus of the stomach is reduced to a negligible amount Hypersecretion of gastric juice of nerv ous origin with ulcer formation can be produced in vagus innervated total pouch dogs by draining the gastric secre tion to the exterior instead of into the intestinal tract A similar hypersecretion with ulcer formation but due to hyper function of the gastric antrum may be produced by transplant ing the antrum into the colon

Hypersecretion of gastric juice is regularly found in pa tients with duodenal or gastrojejunal ulcers This is pre dominantly of nervous origin and may be reduced to normal or subnormal levels in 97% of patients by an adequate trans abdominal supradiaphragmatic section of the vagus nerves Removal of the gastric phase of secretion in duodenal ulcer patients by antrum resection is not regularly followed by great reduction in secretion and the high incidence of stoma ulcer after this procedure is further evidence that hypersecre

(4) J A M A 147 1615 16 0 Dec. 2 1951

appears to be not of purely nervous but also of neurohumoral origin

Late Effects on Gastric Acidity of Subtotal Gastrectomy for Gastric and Duodenal Ulcer Albert Cornell and Leonard Druckerman[3] (Mount Sinai Hosp New York City) reviewed 154 histories which recorded one or more Rehfuss test meals given three or more months after surgery since 1937 No patient had previous surgery other than closure of a perforated ulcer in a few instances Unless definite evidence of ulcer was found at operation or in the resected specimen the history was not surveyed

Bleeding episodes were recorded in one third of the cases and perforation in 10% Nine benign lesser curvature or juxta esophageal ulcers were treated by resection below the ulcer Postgastrectomy achlorhydria was found in 55% of duodenal ulcer patients and in 36 of 40 with gastric ulcer Three of the remaining four with gastric ulcer tested with a gruel meal showed achlorhydria which was corrected with histamine Changes in established pattern were noted in 12 duodenal ulcer patients Six with acid three or more months after surgery later had achlorhydria whereas six others with achlorhydria three or more months after operation later had free acid This represents a change in either direction in about 10% of the duodenal ulcer group Thus in 90% of patients one may expect test results three months postoperatively to be the same many years later

Results were unsatisfactory only among duodenal ulcer patients with acid after surgery Of 114 patients with duodenal ulcer 51 had free acid postoperatively of whom 9 had pain or bleeding 4 proved to have jejunal ulcers whereas 5 had one or more painless hemorrhages without x ray evidence of ulcer One had hiatus hernia and one prolapse of the afferent loop into the stomach

Three of the four jejunal ulcer patients had high preoperative acid levels Of 51 patients with free acid postoperatively about 1 in 13 developed jejunal ulcer and 1 of 6 developed jejunal ulcer gastritis jejunitis or complication producing massive hemorrhage Reoperation was necessary in four Simultaneous infradiaphragmatic vagotomy with gastrectomy for duodenal ulcer has been shown to increase the incidence of

(3) Gastroent rgy 19 216 23 October 1951

the high incidence of prolapse in patients without symptoms it is concluded that the clinical significance of gastric prolapse has been overemphasized and is seldom the cause of symptoms

[A timely pertinent contribution, the conclusions of which are in accord with those of a small but experienced group of observers Careful impartial follow up studies on patients operated on for this condition will greatly assist evaluation of its clinical significance —Ed]

Biopsy Study of Chronic Gastritis and Gastric Atrophy R Motteram[6] (Royal Melbourne Hosp Australia) studied biopsy specimens of gastric mucosa from 150 patients with various dyspeptic symptoms in whom an opaque meal revealed



F g 87 —N mal g ri (body) m a. Cyt pl m f m cu se t g ll ta ed nd p tal ll l ghtly ta ed w th ob ou t ll l anal cul P p og g l h f ll da kly ta d. T h m ed ed f m × 150 (Cou t y f M tter m R J P th & B ct 63 389 394 J ly 1951)

no gross abnormality and 43 pernicious anemia patients Normal gastric mucosa is shown in Figure 87 No significant change was seen in the mucosa of 55 dyspepsia patients Changes in the other 95 included (1) superficial gastritis without atrophy of the tubular epithelium in 45 and (2) gastritis extending into the depths of the mucosa with moderate to severe atrophy in 50 The mucosa of the pernicious anemia patients showed almost complete to total atrophy of chief and parietal cells with no or minimal gastritis

In superficial gastritis the surface epithelium was flattened often forming a syncytium more than one cell thick with

(6) J Path & B ct. 63 389 394 J ly 1951

tion is not of antrum or humoral origin Failure to secure healing of the ulcer or recurrence is usually associated with incomplete vagotomy as evidenced by repeated positive insulin tests six months or more after operation and persistence of nocturnal hypersecretion The percentage of incomplete vagotomies steadily decreases as the surgeon gains more experience but is not eliminated by present technics this constitutes the chief weakness in this method of surgical therapy

[Instructive and frequently quoted observations Dragstedt firmly believes that hyper ecretion is the cause of duodenal and ana tomotic ulcers is the chief factor which prevents their healing and is perhaps exclu ively of nervous origin This conviction is based on observation of ulcer patients who have had complete gastric vagotomy in addition to his studies in experimental animals —Ed]

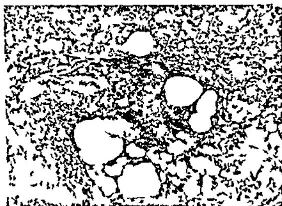
Asymptomatic Gastric Mucosal Prolapse Emanuel J Levin and Benjamin Felson[5] (Cincinnati) performed gastrointe tinal roentgen studies on 100 adults without gastrointestinal symptoms The upper gastrointestinal tract of the fasting patient was examined fluoroscopically with the usual barium water suspension and a minimum of eight spot films of the duodenal bulb were obtained in both upright and recumbent positions Gastric mucosal prolapse was encountered in 18 patients Diagnosis was based on the following criteria concavity of the base of the duodenal bulb mucosal folds passing from stomach to bulb and inconstant deformity of the base of the bulb caused by the varying degree of prolapse

Prolapse was classified as slight i e pronounced concavity of the base of the duodenal bulb and/or definite evidence of gastric mucosa projecting into the bulb for less than 25% of the total bulb area moderate i e gastric mucosa occupying from 25 to 50% of the total bulb area and marked i e gastric mucosa occupying more than 50% of the bulb Ten patients had slight 5 moderate and 3 marked prolapse

The incidence was not significantly affected by any particular systemic disease In a recent unpublished review of 77 cases of acute gastrointestinal bleeding in which upper gastrointestinal series were made without palpation gastric prolap e was found in 19% These findings are at variance with those of Scott who reported an incidence of slightly over 1% in 1 346 symptomatic patients and found no instance of prolapse in 200 injured sailors without gastric complaints Because of

(5) Rad logy 57 514 5 0 October 1951

mucus secreting cells although the base usually showed both chief and parietal cells Active proliferation of foveolar cells produced tortuosity in the pits The surface epithelium was flattened but occasionally showed small budlike syncytial masses There were numerous neutrophilic polymorphonucle ars close to the surface and around the pits Plasma cells were plentiful and in about half the specimens lymphocytes were aggregated into follicles near the mucosal base In two speci



F g 89 —G t ti w th tr phy f t b l h w g d po t asso- t d w th lymph d collect Hemat yl eo ed ed f m × 150 (C urte y f M tte am, R. J P th & B ct 63 389 394 J ly 19 1)

mens adipose tissue was present probably developing through involution of these follicles (Fig 89) Mucosal depth was re duced to two thirds to three fourths of normal Small patches of intestinal epithelium were noted in about half the specimens showing evere mucosal atrophy

Thinning of the mucosa was invariable and often extreme in pernicious anemia specimens being reduced to half its normal depth in 30% Chief and parietal cells were absent in 90% the tubules being lined by mucus secreting neck cells or intestinal type epithelium There was rarely any evidence of gastritis Adequate liver extract therapy failed to alter the abnormal mucosal pattern

[A welcome contr bution to our knowledge of the histopathology of a heretofore somewhat unfamiliar and controversial entity —Ed]

indistinct cell borders and hyperchromatic nuclei The appearance was one of recent epithelial regeneration occasionally plainly beginning in the foveolae The function of mucus secretion was poorly developed in these cells The superficial portion of the lamina propria showed dense infiltration with wandering cells Mucus secreting neck cells extended down the tubules due either to failure in normal differentiation

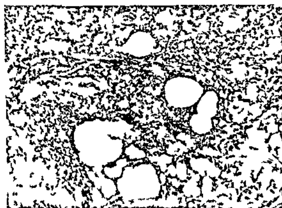


Fig 88—Sup [illegible] with num [illegible] lamina propria [illegible] length [illegible] hang [illegible] two [illegible] darkly with muc [illegible] × 140 (Courtesy [illegible] R [illegible] J Path & Bact 63 389 394 July 1951)

into pepsin secreting cells or to actual change from pepsin to mucus secretion in already differentiated cells (Fig 88) When the damaging agent was known as in alcoholics and removed the gastric mucosa returned to normal in about two to three weeks Repeat biopsy revealed no evidence to suggest inevitable progression of a superficial to a more atrophic gastritis

In gastritis with moderate to severe atrophy it was found that the full length of the tubules may become lined with

mucus secreting cells although the base usually showed both chief and parietal cells Active proliferation of foveolar cells produced tortuosity in the pits The surface epithelium was flattened but occasionally showed small budlike syncytial masses There were numerous neutrophilic polymorphonucle ars close to the surface and around the pits Plasma cells were plentiful and in about half the specimens lymphocytes were aggregated into follicles near the mucosal base In two speci



Fg 89—G t t wth tr phy f t b l h w g d p e t asso t d w th lymph d ll t on H m t ꝫ l n n d d f m × 150 (C t y f Mott m R J P th & B ct 63 389 394 J ly 1951)

mens adipose tissue was present probably developing through involution of these follicles (Fig 89) Mucosal depth was re duced to two thirds to three fourths of normal Small patches of intestinal epithelium were noted in about half the speci- mens showing severe mucosal atrophy

Thinning of the mucosa was invariable and often extreme in pernicious anemia specimens being reduced to half its normal depth in 50% Chief and parietal cells were absent in 90% the tubules being lined by mucus secreting neck cells or intestinal type epithelium There was rarely any evidence of gastritis Adequate liver extract therapy failed to alter the abnormal mucosal pattern

[A welcome contribution to our knowledge of the histopathology of a heretofore somewhat unfam l ar and controversial entity —Ed]

Value of Gastric Biopsy in Study of Chronic Gastritis and Pernicious Anemia Ian J Wood[7] (Melbourne) presents observations based on a study of gastric mucosa specimens obtained with a flexible gastric biopsy tube The instrument consists of a length of Bowden wire covered with plastic tubing to make it airtight At the distal end is a metal cylinder housing a cylindric knife which can be moved up and down past a lateral hole by means of a wire which passes through the entire length of the instrument The tube can be passed easily into the empty stomach Negative pressure exerted on the upper end sucks a knuckle of gastric mucosa through the hole where it is cut off by pulling up the knife The procedure which causes little inconvenience yields a bit of mucosa 2 mm in diameter and extending to the muscularis mucosae The specimen is usually taken from the greater curvature of the body of the stomach Complications following biopsy have been few In 552 biopsies on 462 patients there was no evidence of perforation or established ulceration Hematemesis or melena occurred in six instances but on no occasion seemed to threaten life

Three main types of lesion were found classified histologically as superficial gastritis atrophic gastritis and gastric atrophy In two cases representative of the superficial gastritis group symptoms consisted of flatulent dyspepsia and hypochlorhydria or achlorhydria and in one case there had been a gastroduodenal hemorrhage It appears that gastritis may lead to recurrent gastric bleeding and possibly to the anemia seen in Witts anemia It may resolve especially if the causal factor such as acute alcoholism is removed If so there is improvement in symptoms level of free acid and biopsy picture

Superficial gastritis may also progress to atrophic gastritis with persistent achlorhydria and more pronounced symptoms Once this stage is reached there is little or no tendency to resolution Here there is atrophy of the acid and pepsin secreting cells in addition to the inflammatory reaction This condition may cause recurrent flatulent dyspepsia atrophy of the tongue and constant hypochlorhydria or more often achlorhydria A barium meal test may give negative results

(7) B M J 2 823 825 Oct 6 1951

There may be hypochromic anemia due to mucosal blood loss malnutrition and impaired iron absorption Wood found little or no evidence that this type of gastritis is associated with pernicious anemia or subacute combined degeneration of the cord a common characteristic of gastric atrophy

Findings in pernicious anemia included (1) severe atrophy of the gastric mucosa with some intestinal metaplasia (2) almost complete absence of inflammatory change (3) no regeneration with standard liver therapy for several years and (4) no regeneration with liberal weekly injections of vitamin B_1 In three cases of probable subacute combined degeneration of the cord with normal peripheral blood and bone marrow the changes in the gastric mucosa were identical with those in pernicious anemia Severe gastric atrophy without inflammatory change may well be a slow atrophic process of different etiology Much has yet to be learned of the etiology course and prevention of superficial gastritis atrophic gastritis and ga tric atrophy

[The histopathologic finding are in accord with those reported by Motteram in the preceding article Some critici m could be raised as to the procedure because the specimen must be taken rather blindly and only a small portion of gastric mucosa is available for study Ho ever Eddy Palmer (Am J M Sc 219 648 1950) found the biopsy tube safe and efficient and the pecim ns atisfactory —Ed]

Morphologic State of Gastric Mucosa in Duodenal Ulcer Patient. Eddy D Palmer[8] (Walter Reed Gen l Hosp) studied 350 duodenal ulcer patients to determine incidence and importance of the gastritides in this disease and to observe the effect of coexistent gastritis on response to ulcer therapy Data were obtained by hospital observation gastroscopic study and examination of gastric mucosa biopsies Mucosa appeared normal gastroscopically in 70% of 150 patients with nonobstructing active duodenal ulcers the rest showing chronic hypertrophic or superficial gastritis Among 150 patients with inactive duodenal ulcers stomachs were normal in 58% all three common types of chronic gastritis were noted in the rest Greater incidence of chronic hypertrophic gastritis in the latter group may have been correlated causally with symptoms which brought these healed ulcer patients to the physician When compared with a group of dyspeptics

(8) G t oe te l gy 18 6 0 May 1951

without ulcer the 500 nonobstructed patients showed a significantly greater incidence of superficial gastritis and a decreased incidence of atrophic gastritis There was no correlation between duration of ulcer history and incidence of gastritis

Histologically biopsies from 34 patients revealed normal gastric mucosa in 19 and complex but classifiable abnormalities in the others Serial biopsies in two cases showed no changes in the histologic picture over periods of three and seven months Of 50 additional ulcer patients with obstruction and gastric retention three fourths showed chronic gastritis Although it was usually impossible to determine whether a coexistent gastritis and/or the ulcer caused the patient s symptoms poor response to therapy was closely correlated with presence of one of the chronic gastritides and with length of ulcer history

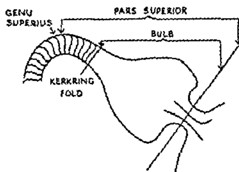
It is concluded that greater incidence of chronic superficial gastritis in nonobstructed duodenal ulcer patients may result from gastric hypermotility of the ulcer state Chronic atrophic gastritis with attendant interference with secretory activity is rare in the duodenal ulcer patient and when present protects against ulcer activation Pyloric obstruction is usually accompanied by gastritis on a simple traumatic basis Chronic gastritis is an important factor in the poor symptomatic response of the treated ulcer patient

Postbulbar Duodenal Ulcers Eric Samuel[9] (Johannesburg) reports 12 cases Such ulcers may present a clinical entity sufficiently clearcut so that they may be differentiated from peptic ulcers occurring elsewhere The portion of the duodenum from the pylorus to a point at which it alters its horizontal direction to a vertical course is called the pars superior the actual bend being known as the flexure (genu superius) (Figs 90 and 91) The duodenal bulb is that portion of the pars superior between the pylorus and the first Kerkring fold This point is fairly easily recognized in the normal subject since the mucosal folds of the duodenal bulb are normally four in number and run parallel to the long axis of the duodenum The point at which these longitudinal folds meet the first transverse fold forms the apex of the bulb

Among the 12 patients males predominated (ratio of 5 1)

(9) So th Afri n M J 26 121 1 5 F b 16 1952

Patients were aged 22 82 Average age was 54 which is considerably higher than that for patients with ulcers in the duodenal cap itself probably because many of the patients went long periods without a diagnosis Five had histories extending over more than 5 years and two over 12 and 14





F g 90 (t p) —B u d f bulb P th lb p t n f pa pe f duod m w th t t f ld t nd g f m pe f bulb to g n per s f d od m
F g 91 (bottom) —T n t n th gh bd m n t le t f pylorus N t b kw d d t n f p s p f d od m.
(C le y f S m l E S u h Afric n M J 6 1 1125 F b 16 1952)

years Pain tends to radiate through to the back and right scapular region This pain can occur when ulcers in the duodenal cap penetrate into the posterior abdominal wall but penetration (and consequently this symptom) is commoner in patients with postbulbar ulcers Seven of the 12 *patients had this symptom Three had been investigated for* spinal disease because of the severity of backache Absence of any definite periodicity of pain food relation in patients

with these ulcers is especially misleading only half the patients having a direct relationship A high proportion of patients had nocturnal pain In most alkalis gave temporary relief Likewise those put on an ulcer diet improved initially but relapsed later

Postbulbar ulcers have a pronounced predisposition to either melena or hematemesis The melena may be severe or occult Initially five patients had severe melena or hematemesis Several patients had repeated hemorrhages and many had previous barium meal examinations with negative results The other symptoms vary In some patients weight loss is sufficiently striking for malignancy to be suspected Nausea and vomiting are not prominent Obstructive symptoms are not severe even in those patients with long histories and strictures of the duodenum apparently do not occur

The x ray features are identical with those of ulcers in the duodenal cap ulcer crater and associated spastic deformity To some extent dimensions of the crater depend on chronicity of the case in long standing cases it may attain an enormous size and may then mimic a diverticulum Spasm of the duodenum around the crater is frequent The more distal the ulcer in the second part of the duodenum the greater the spasm The spasm may be local (on the wall opposite the crater) or reflex at the pylorus Demonstration of persistent spasm of the duodenum in the postbulbar portion of the pars superior or second portion is of utmost importance as in many patients the actual ulcer crater cannot be visualized Localized spasm in this portion of the duodenum is always significant if demonstrated with any degree of constancy it may be regarded as almost sufficient evidence for diagnosis

These ulcer craters have great propensity to burrow into the head of the pancreas and posterior abdominal wall Even with adequate medical treatment the tendency to recurrent hematemesis and chronic invalidism is great Treatment should therefore be partial gastrectomy Actual removal of the ulcer crater is difficult In most patients treated surgically a modification of partial gastrectomy was done in which the mucosa was removed from the duodenum

[On previous occasions we have stressed the fact that the postbulbar ulcer could be rather easily overlooked Samuel believes compres

sion studies taken in the erect position are seldom as helpful as films t ken in the right lateral and slightly off prone position to demonstrate the entire length of the pars superior The following article is an in truc tive contribution on the same subject —Ed]

Postbulbar Duodenal Ulceration. Warren M Lonergan and Alfred Kahn Jr[1] (Barnes Hosp) in reviewing the records of about 75 000 hospital admissions during 1940-47 found only 10 cases of peptic ulcer of the di tal duodenum This portion of the duodenum is considered to begin 5 cm beyond the pyloric ring In seven cases the ulcer was on the posterior and in one on the anterior wall Eight ulcers were confirmed at operation of these two were proximal to the common bile duct and five were at the level of and one was di tal to the ampulla Six ulcers of the posterior wall had perforated into the head of the pancreas and the seventh had perforated laterally producing a mass of adhesions which effectively walled it off Associated ulcer in the cap was found in two cases All patients were males aged 18 70 (average 45½) Duration of symptoms ranged from several days to over 29 years

Symptoms were similar to those of bulbar ulcer Pain appearing two to four hours after meals and at night was the commonest complaint It was relieved by food and ant acids As the lesion progressed failure of pain to respond to food and antacids and change in the characteristic cycle were noted Seven patients had massive hemorrhage with hematemesis and/or tarry stools Other symptoms included flatulence eructation pyrosis nausea vomiting and weight loss One patient had transient jaundice and fever associated with severe right upper quadrant pain The only consistent physical finding was variable tenderness in the epigastrium and right upper quadrant

Diagnosis was made primarily by x ray A definite crater on the inner aspect of the second portion of the duodenum was seen in four cases (Fig 92) In a fifth a persistent fleck of barium was noted at the ampulla of Vater The niche is usually small hemi pherical or oval and slightly irregular Infrequently an incisura may be seen More often there are narrowing and constriction of the bowel lumen at the level of the ulcer with the appearance of a filling defect This

(1) G t oe te l gy 17 494 503 Ap il 1951

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Gastric Antacid and Antisecretory Drugs Survey Based Primarily on Their Effects on Gastric Secretion in Man The goal of therapy with these drugs presumably is effective neutralization or inhibition of the free acid and peptic activity of gastric secretion Effective neutralization is defined as maintenance of pH of 4 0 5 5 or higher adequate inhibition as complete absence of free acid for three to six hours or longer A survey by Joseph B Kirsner Walter L Palmer Erwin Levin and Arthur B Klotz (Univ of Chicago) *showed that none of the available antacids completely neutralizes free acidity in man for prolonged periods* Relatively large quantities 10 20 times greater than necessary for in vitro experiments are required to lower free acidity for brief periods probably because of gastric emptying and the continued secretion of acid

Calcium carbonate is apparently the most effective antacid *in current use Continuous intragastric drip is perhaps more* effective than hourly doses to control the excessive nocturnal secretion of duodenal ulcer but it is not practical for general or prolonged use and is contraindicated in pyloric obstruction Aluminum hydroxide magnesium trisilicate or tribasic calcium phosphate in large quantities diminish but do not eliminate free acidity their neutralizing effect is much less or nil when administered at long intervals and in small amounts The efficiency of sodium carboxymethylcellulose in man remains to be determined Protein hydrolysates are less effective than calcium carbonate even in large amounts and provoke a secondary rise in secretion exceeding original levels Anion exchange resins may partially reduce gastric acidity in man they do not seem superior to other antacids and are less effective than calcium carbonate Detergents such as sodium alkyl do not alter the pH of the gastric contents and their antipeptic action in man is insignificant Mucin has little neutralizing value because of the peptones in the preparation and not because of the mucin per se

Antihistamines do not depress and may stimulate gastric secretion in man Moreover antihistamine therapy may be complicated by agranulocytosis The antisecretory effect of current enterogastrone concentrates is variable and unpredictable Hormones such as parathyroid extract desoxy

(2) A I t M d. 35 785 811 O t be 1951

was found in all cases The mucosal pattern is often distorted with loss of the fernlike pattern characteristic of the duodenum Tenderness may be localized to the site of the de-

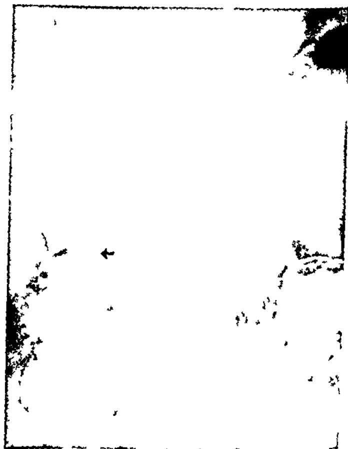


Fig 92 —Sharply defined ulcer crater in second portion of duodenum on medial border Lumen narrowed and there is incisura opposite crater (Courtesy of Lonergan W M and Kahn A J Gastroenterology 17 494 503 April 1951)

formity When the ulcer is adjacent to the duodenal cap the latter tends to be small and irregularly filled

More complete x ray examination would lead to earlier diagnosis and reduce the incidence of hemorrhage perforation and stenosis

and then usually 50 mg with each meal and 50 or 100 mg at bedtime They were permitted a regular diet without intermediate nourishment and most received no additional medication

Results were encouraging 97 patients had prompt and lasting relief many for the first time on any regimen Relief usually began in two or three days Seven had lesser degrees of relief six were treated who were asymptomatic but had x ray evidence of ulcers not responding to a Sippy type regimen Toxic reactions necessitating discontinuance of therapy in two were excessive dryness of mouth urinary frequency and slowing of the stream acute urinary retention and difficulty in visual accommodation One of two patients not benefited by banthine® required surgery Symptoms definitely increased in two patients who had cicatricial duodenal stenosis with obstruction they later required surgery One patient who had relief for five months had a recurrence while still on banthine® and subsequently required surgery Thus surgery was necessary in only four one other patient elected to have surgery because of three previous episodes of massive bleeding Progress examinations by x ray and fluoroscopy revealed healing of the ulcer in 55 of 69 patients with definite improvement in 9 others

Banthine® was given similarly to 20 patients with other diseases 6 of 9 with hyperacidity syndrome 2 with marginal ulcers and 2 with ulcers in hiatus hernias obtained excellent relief Results were unsatisfactory in four patients with gastric ulcer one of whom obtained some symptomatic relief although x rays revealed no changes At operation malignancy was found The drug had no favorable effect on one patient with gastric neurosis one with irritable colon and one with ulcerative colitis It was discontinued because of a skin rash in one patient with hyperhidrosis

Contraindications to use of banthine® are urinary bladder neck obstruction coronary insufficiency and cardiac decompensation glaucoma achalasia and pyloric obstruction If obstruction is due to scarring banthine® is not of use if due to spasm edema and inflammation banthine® is effective after the obstruction is relieved by Sippy treatment

[These conclusions are in general accord with those of Brown and Collins McDonough and O Neil Asher Broders Winkelstein and others

corticosterone acetate and ACTH do not inhibit gastric secretion in vivo Moreover hemorrhage and perforation have been reported in patients with known or unsuspected peptic ulcer during ACTH therapy

Atropine produces extremely variable effects in duodenal ulcer patients and in effective doses is usually accompanied by toxic symptoms its principal usefulness may be to enhance the degree of antacid neutralization by prolonging gastric emptying Synthetic atropine like compounds offer no particular advantage and are less effective than atropine However other cholinergic blocking agents have produced promising results Tetraethylammonium salts significantly depress gastric secretion and motility in man temporarily but produce undesirable side reactions their use is contraindicated in severe hypertension and renal disease and probably in massive hemorrhage Hexamethonium compounds have given promising preliminary results although the postural hypotension and syncope produced may render them unsuitable for ambulant patients Banthine® parenterally appears to induce greater inhibition of gastric secretion with fewer toxic manifestations However recurrences of peptic ulcer have been noted in several patients during banthine® therapy This drug is contraindicated in existent or incipient glaucoma and in prostatic hypertrophy it should be given cautiously or avoided in patients with coronary insufficiency and other cardiac disorders A longer observation period is required for complete evaluation of this and similar compounds

Newer cholinergic blocking agents are becoming available for clinical trial Continued exploration of hormonal factors and of drugs acting on enzyme systems possibly implicated in the mechanism of gastric secretion and the further development of cholinergic blocking agents may yet lead to synthesis of an effective and safe compound for sustained elimination of free acid

Use of Banthine® in Treatment of Duodenal Ulcer Preliminary Report on Its Use in 137 Patients is made by Charles H Brown and F N Collins[3] (Cleveland Clinic) In 117 patients who had duodenal ulcer average duration of symptoms was 5 9 years 39 had already had complications Patients were given 100 mg banthine® every six hours for two months

(3) Gastroenterology 18 26-35 May 1951

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The contraindications and the nature of the unfavorable reactions are generally known Toxic psychosis has been reported but is rare Winkelstein observed that about 12% of patients refused to continue the drug this incidence was reduced to 2% when treatment was begun with 25 mg doses for three days and then dosage increased to 50 mg if unfavorable reaction was mild or absent The drug was taken 15 30 minutes before each meal on retiring and once during the night if the patient was awake

The prompt pain relieving of banthine® is usually striking The unpleasant taste is somewhat trying From the standpoint of animal experimentation and clinical observation authorities are somewhat at variance as to the degree of its pharmacologic superiority over belladonna and its derivatives Banthine® is an adjuvant to conventional methods of therapy not a replacement or substitute therapy —Ed]

Clinical Evaluation of Methantheline (Banthine®) Bromide in Gastroenterology Results obtained by G Gordon McHardy Donovan C Browne Frank H Marek Robert McHardy and Swan Ward[4] (New Orleans) indicate that banthine® is an effective and relatively safe anticholinergic a valuable adjunct to management of many gastrointestinal disturbances characterized by hypersecretion and hypermotility Clinically it is superior to atropine as an antispasmodic

After administration of the drug salivation was definitely inhibited in 86% of 200 patients Inhibition was directly related to sensitivity of the patient and dosage of the drug The effect was transient tolerance often being acquired within 72 hours A similar effect was noted in 10 patients with infectious parotitis Banthine® parenterally 100 mg every four hours resulted in a decrease in the volume of gastric secretion in 10 normal men in 10 with active acute duodenal ulcer and in 10 with chronic duodenal ulcer In 10 additional patients the secretory response to insulin hypoglycemia and to histamine stimulation was unmodified except for a slight diminution in volume An inconstant but definite secretory depression was noted in 10 patients with active duodenal ulcer accompanied by pronounced nocturnal pain When 1/75 gr atropine and 50 mg bentyl® hydrochloride were used as equivalent to 100 mg banthine® they were of approximate efficiency in volume secretory depression and like banthine® without influence on titratable acidity

Banthine® did not affect the fistula output of 4 patients with duodenal and 3 with jejunal fistulas but decreased that of 10 ileostomy patients an average of 33% There was a

(4) J A M A 147 1620 1626 Dec. 22 1951

dramatic inhibition of fistulous drainage averaging 60% in five patients with pancreatic fistulas who were given 100 mg banthine* parenterally every four hours for three days all recovered In addition four patients with choledochostomy drainage after cholecystectomy for choledocholithiasis showed an average increase in bile excretion to 240 cc in 24 hours after administration of the drug

As anticipated the hypertonicity of esophageal spasm was accentuated by administration of banthine* Radiographic studies 30 minutes after subjects were given 100 mg intramuscularly revealed delayed emptying of barium into the duodenum and sluggish ineffective peristaltic waves Gastroscopy confirmed the radiographic findings of cessation of peristalsis and atony of the gastric wall No beneficial effect was noted after administration of the drug to 17 patients with regional enteritis However in 10 with assumed hyper peristaltic diarrhea in whom the barium transit time to the ileocecal valve was less than 90 minutes banthine* prolonged the transit time to an average of 256 minutes with amelioration of the diarrhea from an average of 12 to 4 stools/24 hours Actual colon disease entities such as diarrhea concomitant to neoplasm and hypermotility diarrhea of the various forms of chronic ulcerative colitis were not influenced In the severe irritable colon syndrome in which both hypersecretion and hypermotility contributed to cause a persistent diarrhea with copious mucous and fluid stools 400 mg banthine* daily had a limited but favorable effect This did not extend beyond the treatment period nor did it prevent recurrences

Sixty ambulatory patients with duodenal ulcer were treated with banthine* plus the usual diet and symptomatic measures 100 mg was taken orally every six hours until the patient was asymptomatic then 50 mg before meals and 100 at bedtime After an 18 month follow up results were compared with those in two control series one managed by an acceptable ambulatory ulcer regimen plus a placebo and the other by inadequate doses of atropine only The percentage of cures in experimental and control groups did not vary appreciably from results obtained in a previous evaluation of ulcer patient management Symptomatic reactivation during therapy was not unusual

The authors concluded that despite the dramatic influence

of banthine® in achieving pain relief the basic principles of ulcer management should not be discarded

Peptic Ulcer Medical Cure by Efficient Gastric Acid Neutralization is reported by N E Rossett F H Knox Jr and S L Stephenson Jr [5] (V A Hosp Memphis Tenn) A total of 1 585 patients were treated

METHOD —Two antacid preparations were used When the stomach contained protein (immediately postprandially or during a hemorrhagic episode) or the patient was unable to tolerate the other type a mixture of 0 9 Gm calcium carbonate and 0 1 Gm. magnesium oxide in 200 cc milk was given When little or no protein was present (usually the case when antacids were administered 45 cc of a mixture of aluminum hydroxide gel (5 5%) 4 parts by volume and milk of magnesia (USP) 1 part by volume was used Buffering action of the former lasted about four hours of the latter six hours

The ulcer diet omitted gastric secretagogues and coarse very hot or very cold foods Overdistention was avoided The diet provided all essential food elements for maximal nutrition including 100 150 Gm protein daily

Schedule for treatment of uncomplicated peptic ulcer included bed rest ulcer diet with 50 mg ascorbic acid daily aluminum hydroxide milk of magnesia mix between meals 8 p m bedtime and every two hours through 6 a m 1 5 cc tincture of belladonna every six hours increased by 0 5 cc steps cautiously as required Acid neutralization was determined by gastric emptying with an Ewald tube at 8 a m before feeding the patient lying in the prone Trendelenburg position Free achlorhydria was tested for with Topfer s reagent (pH 3 4 5) Antacids were increased to 150 cc every two hours as required to obtain neutralization Bed rest was continued for five days after all pain had ceased

Patients with bleeding peptic ulcer were put at bed rest and barbiturates given for sedation A modified Meulengracht regimen was carried out (soft bland foods every two hours during the day) and the calcium carbonate magnesium oxide mix was added to feedings every two hours throughout the night Tincture of belladonna 1 5 cc or atropine 1 mg every six hours was given the latter if vomiting occurred Gastrointestinal series was done within the first four days

For peptic ulcer with obstruction the stomach was drained at 8 a m and 10 p m as described and a meal or milk and alkali were given at once In addition a liquid diet of skimmed boiled milk was given each hour the amount/feeding being the quantity passed through the obstruction/day divided by the number of daily feedings Feedings were started at 8 a m and ended at 10 p m Tincture of belladonna was used Neutralization was achieved at night by giving the aluminum hydroxide milk of magnesia mixture

(5) An t M d 36 98 109 Ja u) 195

as determined by acidity of the 8 a m specimen Electrolyte balance was restored and nutrition supplemented if indicated by parenteral administration of saline solution dextrose and amino acids When 3 000 cc milk emptied normally soft foods such as soft boiled eggs Cream of Wheat etc were added until the patient could tolerate a full ulcer diet

In all of 1 288 consecutive patients with uncomplicated peptic ulcer this therapy stopped ulcer pain and produced healing In only two patients did pain persist more than 14 days after therapy In both x rays and operation revealed a healed ulcer Residual pain was therefore believed to be psychogenic There were two deaths in 168 episodes of severe bleeding *without autopsy or x ray confirmation of ulceration* All who survived had x ray confirmation of niche of niche and constant deformity or of constant deformity alone Criterion for bleeding was hospital verified gross hematemesis with grossly tarry stools or the latter alone with x ray confirmation of ulceration in both groups

Ulcer history of over four years was present in 1 024 cases There were 237 Negro patients in whom the only difference was more bizarre localization of pain Eighty four gastric 1 493 duodenal 6 jejunal 1 gastric and duodenal and 1 duodenal and jejunal ulcer were treated There were 314 readmissions Night pain appeared in 41% of the patients most often before 2 a m Time necessary for pain to disappear completely was decreased by increasing the amount of antacid used during the night All demonstrable craters healed in 6 weeks average 2 16 In the bleeding group transfusions were used freely *Only three needed emergency surgery all survived* There were 129 patients with obstruction in all but 3 opening was sufficient to achieve positive nitrogen balance and weight gain Later 72 underwent surgery

Dosage of tincture of belladonna was increased up to 4 cc every six hours in selected young patients Blurred vision and dry mouth were met with reassurance Toxic psychosis occurred in only 3 of 694 patients so treated in none given *single doses over 1 5 cc Mild dysuria occurred in 11* mainly in the older age group Because of fear of glaucoma patients over 45 received only 1 5 cc every six hours

An additional 141 patients with duodenal and 5 with gastric ulcer were similarly treated except that 100 mg banthine[*] every four hours was used instead of belladonna All were

of banthine® in achieving pain relief the basic principles of ulcer management should not be discarded

Peptic Ulcer Medical Cure by Efficient Gastric Acid Neutralization is reported by N E Rossett F H Knox Jr and S L Stephenson Jr (V A Hosp Memphis Tenn) A total of 1 585 patients were treated

METHOD —Two antacid preparations were used When the stomach contained protein (immediately postprandially or during a hemorrhagic episode) or the patient was unable to tolerate the other type a mixture of 0 9 Gm calcium carbonate and 0 1 Gm. magnesium oxide in 200 cc milk was given When little or no protein was present (usually the case when antacids were ad ministered 45 cc of a mixture of aluminum hydroxide gel (5 5%) 4 parts by volume and milk of magnesia (USP) 1 part by volume was used Buffering action of the former lasted about four hours of the latter six hours

The ulcer diet omitted gastric secretagogues and coarse very hot or very cold foods Overdistention was avoided The diet provided all essential food elements for maximal nutrition including 100 150 Gm protein daily

Schedule for treatment of uncomplicated peptic ulcer included bed rest ulcer diet with 50 mg ascorbic acid daily aluminum hydroxide milk of magnesia mix between meals 8 p m bedtime and every two hours through 6 a m 1 5 cc tincture of belladonna every six hours increased by 0 5 cc steps cautiously as required Acid neutralization was determined by gastric emptying with an Ewald tube at 8 a m before feeding the patient lying in the prone Trendelenburg position Free achlorhydria was tested for with Topfer s reagent (pH 3 4 5) Antacids were increased to 150 cc every two hours as required to obtain neutralization Bed rest was continued for five days after all pain had ceased

Patients with bleeding peptic ulcer were put at bed rest and barbiturates given for sedation A modified Meulengracht regimen was carried out (soft bland foods every two hours during the day) and the calcium carbonate magnesium oxide mix was added to feedings every two hours throughout the night Tincture of belladonna 1 5 cc or atropine 1 mg every six hours was given the latter if vomiting occurred Gastrointestinal series was done within the first four days

For peptic ulcer with obstruction the stomach was drained at 8 a m and 10 p m as described and a meal or milk and alkali were given at once In addition a liquid diet of skimmed boiled milk was given each hour the amount/feeding being the quantity passed through the obstruction/day divided by the number of daily feedings Feedings were started at 8 a m and ended at 10 p m Tincture of belladonna was used Neutralization was achieved at night by giving the aluminum hydroxide milk of magnesia mixture

(5) Ann Int Med 36 98 109 Jan 1952

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pain free within 14 days Comparison showed that banthine* relieved pain more promptly but there was no statistical difference in average healing time Complaints of blurred vision and dry mouth were less but four patients one with prostatism had to be changed to belladonna because of severe urinary retention Patients with obstruction did better with belladonna probably because banthine* caused greater depression of gastric motility

All patients were required to attend classes in ulcer management given by the physician and dietitian The diet was usually started on the day of hospitalization The patient was therefore on the diet he was expected to follow the rest of his life surgeon radiotherapist or psychiatrist not intervening

[Strikingly successful results followed treatment skilfully planned and meticulously carried out Thus adequate control of the corrosive action of the acid gastric secretion was obtained further confirming the importance of Sippy s concept in therapy The encouraging outcome even in patients with complicated lesions strengthens the conviction that no ulcer should be considered refractory until a carefully planned intensive medical regimen has been carried out —Ed]

Treatment of Peptic Ulcer Any remedy for peptic ulcer should be evaluated for (1) the immediate symptomatic relief (2) its influence in healing the lesion and (3) its ability to change the natural course of the disease Using these criteria John W Todd[6] found only three methods of proved value—diminishing the gastric acidity gastrectomy and psychotherapy Gastric acidity can be diminished either by diet or by giving alkalis Frequent small feedings particularly milk and milk dishes may be advisable for those few patients with a deep seated distrust of drugs There is no proof that avoidance of certain foods thought to be irritating is beneficial unless they cause immediate distress Use of alkaline tablets is as effective in neutralizing acidity and enables the patient to lead a more normal life than special diets While carrying on usual activities the patient should take two 7 gr tablets of aluminum hydroxide or other alkali hourly throughout the day except at the usual mealtimes If he wakes at night he should take 2 tablets This program should continue until the ulcer is proved healed by either radiography or gastroscopy or in the case of a duodenal

(6) La c 1 113 118 Jan 19 1952

ulcer by continued absence of symptoms it should be resumed during periods of mental stress or when symptoms recur

The large number of gastrectomies performed to date and the many long follow ups indicate that a high proportion of patients who have had this operation remain free from peptic ulcers indefinitely However there is no guarantee of cure and operative mortality is considerable as is incidence of the postgastrectomy syndrome Aside from such indications as recurrent hematemesis and pyloric stenosis a reasonable criterion for operation is that the patient cannot be made and kept well by frequent doses of alkali while living a normal life Gastroenterostomy is the operation of choice for pyloric stenosis especially in old and feeble patients since anastomotic ulceration is unlikely to develop and they may die after gastrectomy Vagotomy combined with gastroenterostomy may be of value in duodenal ulcer

Psychotherapy although attractive in theory is severely limited in application It may be valuable because a patient is emotionally upset not so much because it may favorably influence the course of an ulcer

Todd suggests that the advocates of such orthodox methods as bed rest absence from work an artificial and monotonous diet phenobarbital the eradication of septic foci and the avoidance of tobacco and alcohol should be required to prove their views until such proof is obtained it is sound practice not to prescribe these remedies for peptic ulcer

{During the past five years articles in British medical journals and in at least one American text have challenged the principles underlying orthodox or conventional methods of medical treatment Such treatment it is claimed does not alter the life history of the disease polypharmacy and bed rest are decried as noted in this article and dietetic treatment as practiced at present does not hasten healing and may retard it. Though one should keep an open mind in such matters it is to be seriously doubted that the rank and file of the profession are in accord with these pronouncements I have observed too many patients with crater form lesions respond unsatisfactorily to this or that new vogue in treatment or to a half hearted, incomplete conventional regimen intensive hospital therapy on the other hand resulted in prompt disappearance of the crater and firm healing We have known for years that ulcers heal spontaneously and that even active ulcers may be permanently symptomless the problem concerns that estimated 25% of ulcer patients with sufficient persistent or recurring trouble to come under our purview Usually it is the patient rather than the ulcer that is refractory The problem is not so much one of healing the ulcer with the methods at our disposal but of keeping it healed and that problem is not insurmountable In the light

of present knowledge a justifiable polypharmacy is restricted to antacids anticholinergic and sedative drugs —Ed]

Factors Influencing Rate of Healing of Gastric Ulcers Admission to Hospital, Phenobarbital and Ascorbic Acid

Richard Doll and Frank Pygott (Middlesex Hosp London) studied 64 patients with uncomplicated and radiographically proved gastric ulcers Half were treated in bed in hospital for four weeks for the first two weeks they were given a moderately strict orthodox diet and for the second week a more liberal one They were then re examined radiographically discharged and advised to continue on a convalescent diet and to return to work when they felt able The out patients were treated from the start the same as hospital patients after discharge Both series were divided into sub groups of four each member of which was allocated at random one of four drug regimens with administration three times daily (1) 50 mg ascorbic acid and ½ gr phenobarbital (2) 50 mg ascorbic acid and an inert tablet (3) ½ gr phenobarbital and an inert tablet and (4) 2 inert tablets Treatment was continued for three months Patients were also given alkaline powders to be taken as necessary for pain All were observed for three months Barium examinations were made at 4 8 and 12 week intervals after the initial study

Inpatient treatment led to a significantly quicker rate of healing as judged by measurements of the ulcer crater and seemed to be more effective in relieving symptoms It is not known whether the therapeutic factor was bed rest or the supervised diet After discharge from the hospital healing usually continued but the evidence that inpatient treatment had a beneficial effect on the subsequent rate of healing is not conclusive Unless the ulcer had healed to one third of its size in one month it was unlikely to heal completely in three The proportion of ulcers which healed completely was small only 8 of the 64 healed after one month and only 17 after three months The giving of phenobarbital and ascorbic acid did not increase the rate of healing

[Apart from treatment methods that may influence the rate of healing Steigmann and Shulman (Gastroenterology 20 20 1952) found that the time required for healing is adversely affected by size and duration of the lesion age of the patient and associated complications such as penetration perforation pyloric obstruction gastritis and hyperacidity —Ed]

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Effect of Banthine® on Disappearance Time of Duodenal Ulcer Craters was investigated by Augustus A Hall Charles J Hornisher and Richard E Weeks[8] (Tokyo Army Hosp) Eighteen patients were treated with modified Sippy diet rest and curtailment of smoking 2 received 100 mg banthine® orally every six hours and 16 100 mg every eight hours A control series of 17 received similar treatment except that aluminum hydroxide was substituted for banthine® Mean average disappearance time of ulcer craters in patients receiving banthine® was 14 4 days compared with 33 7 days in controls Average time for relief from ulcer symptoms studied in 12 patients was 1 hour 47 minutes in 8 1 day in 2 and 10 days in 1 One obtained no relief All of 17 patients observed with regard to side reactions had one or more attributed to banthine® dryness of the mouth 15 blurred vision 7 drowsiness 6 difficulty of urination 5 headaches 3 constipation 2 and bladder paresis 1

[This is an encouraging report Observations on time required to heal crateriform ulcers deal almost exclusively with gastric ulcer notably those of Cummins Grossman and Ivy Ohnell Pollard and associates and Steigmann and Shulman By and large the stomach lends itself better for this type of study than the duodenum Winkelstein (Gastroenterology 0 4'4 1952) reported healing of duodenal ulcer in 43 of 59 patients (73%) apparently treated solely with banthine® No data on the disappearance time of the craters were included but it was noted that one jejunal ulcer healed in six weeks —Ed]

Massive Gastrointestinal Hemorrhage is a serious complication which should never be treated lightly according to Adolph Sachs[9] (Creighton Univ) A definite plan of treatment and constant teamwork by internist laboratory staff and surgeon are necessary Treatment must be individualized Conservative treatment is safe even in patients over age 45 but if such patients have a history of repeated hemorrhages or do not adhere to diet and other instructions operation should be done Occasionally when bleeding fails to respond readily to conservative measures operation is warranted

Massive gastrointestinal hemorrhage may come from any point from the nasopharynx to the anus Sachs is concerned mainly with bleeding from peptic ulcers which represents about 90% of this type of hemorrhage The source of the hemorrhage should be found unless shock is present The

(8) C t oc t loey 18 197 00 J 1951
(9) S b k M J 36 379 38 December 1951

latter should be treated without delay Pallor sweating yawning sighing respiration thready pulse and systolic pressure below 100 are usually signs of impending shock

In well equipped hospitals laboratory tests present no problem but often these are not available While the patient's blood is being typed a complete blood count prothrombin time estimation hematocrit reading blood urea nitrogen determination and urinalysis may be done If 500 cc blood raises the blood pressure to 100 systolic and the pulse rate drops it is safe to watch for developments Careful recross matching with each 500 cc given is important The danger of pulmonary edema is greater when large amounts of blood or fluids are given rapidly The second 500 cc should be given slowly not over 8 cc/minute

Blood loss in acute hemorrhage may be estimated by tilting the body to an angle of plus 75 degrees for three minutes An increase in pulse rate of less than 25 beats/minute indicates negligible blood loss An increase of 30 or more indicates that 1 000 cc blood is needed Development of syncope indicates a need of 1 500 cc and signs of shock in the supine position a requirement of at least 2 000 cc Since glucose and saline solutions are rapidly excreted and diffuse into tissue spaces they do not maintain blood volume or pressure well If a patient is badly dehydrated hypodermoclysis is given with the transfusion With large amounts of citrated blood it is often helpful to give 10 cc of 25% calcium gluconate solution to offset the anticoagulant effect of the citrate

Sachs believes in early feeding in all cases of hemorrhage Opiates are of value in some cases but sometimes cause vomiting and should be used cautiously Barbiturates by hypodermic injection are helpful in lessening apprehension and produce less nausea than opiates Antacids and treatment of high acid curves and night pains and belladonna and other antispasmodics are useful in some cases but should not be used too early Ferrous iron is indicated when tolerated Tobacco is to be avoided and all other medications are used as indicated

Sachs has shown experimentally that fresh and naturally formed clots in dogs withstand full replacement of blood without disturbance

Modern Treatment of Massive Hemorrhage of Peptic Ulcer Origin. Burrill B Crohn and Henry D Janowitz[1] (Mount Sinai Hosp New York City) discuss massive hemorrhage accompanied by shock and decrease of red cell count to 3 000 000 or less and hemoglobin content to below 50% Peptic ulcer hemorrhage is a complication in about 25% of ulcer cases with growing incidence in recent decades Duodenal ulcer incidence is four times that of gastric ulcer hemorrhage from each occurs in the same ratio Initial hemorrhage is often most severe and causes greatest mortality Subsequent massive hemorrhages may occur in 60 74% of patients but are less apt to threaten life Hematemesis is more common in gastric melena in duodenal ulcers Arterial hypertension has little effect on hemorrhage and none on mortality

Medical mortality with conservative therapy of all grave hemorrhage originating in ulcer is 6 9% with only massive hemorrhage tabulated conservative death rate is 10 7% massive hemorrhage after 45 has a 15% fatality rate rising to 50% in the seventies Mortality of hemorrhage from gastric ulcer is twice that from duodenal ulcer Mortality among men exceeds that among women

Results of feeding during hemorrhage as advocated by Meulengracht show a 2 5% mortality rate This includes some mild hemorrhages and Meulengracht feeds less liberally during the critical period—the first 72 hours After that feeding has little significance With more liberal diet restricted to patients with massive hemorrhage mortality rates are better than over all rates with the old starvation and conservative measures

Use of fluid and blood in patients with grave hemorrhage to overcome shock replace excessive blood loss or prepare for surgery is desirable whether directly reflected in lower mortality rates for hemorrhage or not Anoxia from anemia is damaging to the myocardium and may induce coronary thrombosis

Amphogel® intragastric drip gastric suction and administration of Gelfoam and thrombin by mouth have not been much used and evaluation is difficult

(1) C t oe l gr 19 605 6 December 1951

Prognosis in individual cases is difficult If the initial massive hemorrhage ceases within 72 hours prognosis is excellent If initial hemorrhage is followed by recurrent bleeding the outlook becomes increasingly poor Blood urea estimates on successive days have been advocated as an index of gravity of hemorrhage but blood urea values are indicative but not infallible for prognosis The general hypothesis is that the rise in blood urea content is due first to prerenal azotemia then rapid breakdown of body tissues and finally to rapid absorption of digested blood from the upper intestinal tract Shock and resulting diminished circulation through the renal bed in itself increases accumulation of nitrogenous wastes in the blood urea level is thus a measure of circulatory failure

Surgery has been most often used in massive hemorrhage therapy Indications for early surgery are (1) diagnosis of ulcer based on previous history or x ray studies although in some cases hemorrhages have been induced during x ray examination (2) hemorrhage in persons over 45 (3) hospitalization within 48 hours of onset of massive hemorrhage rapidly recurring grave hemorrhage hemorrhage lasting longer than or tending to recur within 72 hours or the need for 1 500 cc blood daily (4) previous grave hemorrhage and now a second massive hemorrhage (5) type of bleeding whether hematemesis (with its higher mortality) or melena (6) degree of severity (red cell count below 3 000 000 and hemoglobin content below 50%) Subtotal gastrectomy with excision of the gastric or duodenal ulcer is the operation of choice When removal of the ulcer bed is difficult exclusion operations may have to be done

Mortality rate for surgery within 48 hours of massive hemorrhage from peptic ulcer in 746 reported cases ranged from 0 to 33% with gross average 10 5% If surgery is delayed until hemorrhage has continued two or three weeks with repeated shock episodes and progressive anemia mortality rate ranges from 4 to 54% averaging 24 4%

Management of Bleeding Gastric and Duodenal Ulcer According to J Englebert Dunphy and Seymour J Gray[2] there is an 85% chance that upper gastrointestinal bleeding is from ulcer or cancer At Peter Bent Brigham Hospital all

(2) Mod Med 90 98 M 1 1952

such patients are treated medically without roentgen study emergency roentgenograms being made preoperatively only when history or previous studies provide no evidence of a surgical lesion The surgeon and internist together follow the patient whose progress is recorded on a chart of pulse blood pressure and respiration Laboratory studies include complete blood studies typing cross matching bleeding clot ting time prothrombin plasma protein blood urea nitrogen chlorides and carbon dioxide a hematocrit reading is repeated every 8 24 hours Guaiac examination is made of all stool specimens

Regarding blood replacement it is necessary to distinguish the exsanguinated from the anemic patient The former con dition is characterized by a short history rapid blood loss and common hematemesis Hematocrit may be normal or only slightly reduced blood volume is low and shock severe These patients require massive transfusions of whole blood Anemia is distinguished by a long history and melena for several days hematemesis is uncommon or minimal and hematocrit low Blood volume is only slightly reduced and shock tran sient Massive transfusions may precipitate pulmonary edema Red cell transfusions are required to raise the hematocrit rapidly *A determination of the circulating red cell volume* is the most reliable guide to rate and extent of hemorrhage Radioactive chromium Cr^{51} a soft x ray emitter with a half life of 26 5 days is a useful and accurate means of measuring the circulating red cell volume during acute hemorrhage

Technic —Radioactive sodium chromate is added in vitro to a mall volume of blood cells where it is rapidly taken up by the erythrocytes Radioactive red cells are then reinjected into the blood tream After they have mixed in the patient s circulation radioactivity of the blood is measured by an x ray end window Geiger Muller counter The circulating red cell volume is calculated by the isotope dilution principle circulating red cell volume (cc) equals total counts injected into circulation divided by counts/cc packed red cells in sample obtained after thorough mixing in cir culation If an unknown amount of blood has been lost after initial red cell volume determination a second injection of tagged erythro cytes is necessary

Patients are fed 100 cc warm milk and cream and 10 cc aluminum hydroxide gel every hour during the day and 200 cc warm milk and cream and 15 cc aluminum hydroxide gel *every two hours during the night* If nausea occurs cream is

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(1) Mod. Med. 92:95, M 1 195_

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(1) Mod Med. 90 98 Mar 1 195

facts have emerged to help clarify problems concerned with treatment, whether medical or surgical

In the first place it seem as illogical for surgeons to submit all patients promptly to operation following manifest bleeding as for physicians to treat all patients medically regardless of severity of hemorrhage Routine surgery would subject most patients to the risk of a procedure not necessary to save life Surgeons themselves have repeatedly stated that medical management carries less risk even in massive hemorrhage if the services of a skilled surgeon are not available Medical treatment exclusively however condemns 10% of patients to death. It is logical to conclude that management is the joint responsibility of practitioner and surgeon alike especially in severe ma sive or exsanguinating hemorrhage

The prevailing problem in the past has been how to single out for emergency operation the patient in whom hemorrhage is likely to be fatal The clinical and laboratory criteria outlined by Dunphy and Gray hould serve as pattern in selection of patients It is perhaps unnecessary to caution the reader that the presence of an ulcer or neoplasm should be fairly established before resorting to surgery In about 20% of patients with single or recurrent episodes of bleeding of varying severity either a demonstrable lesion is not present or it is of a nature in which gastric surgery is not indicated The importarce of such contributing factors as age *location of ulcer delay in operation number of previous hemorrhages* accuracy of diagnosis and associated disease of other organ systems cardiovascular renal in particular varies with individual experience although it is generally agreed that all do have a definite bearing on surgical indication and prognosis —Ed]

ACTH Therapy for Ulcerative Colitis Complicated by Perforation of Coexisting Peptic Ulcer Sol Sloan John D Briggs and James A Halsted[3] (Wadsworth Gen l Hosp Los Angeles) report a ca e

Man 42 was hospitalized because of abdominal cramps and bloody diarrhea Six years previously he had the first symptoms of peptic ulcer and a year later massive bleeding X rays showed a duodenal ulcer and moderately advanced rheumatoid spondylitis The ulcer remained quiescent for three years but in this period chronic recurrent nonspecific ulcerative colitis developed.

On admission he was well developed and nourished weighing 165 lb but appeared moderately ill There was slight tenderness over the descending colon Bloody feces were noted The back showed decided limitation of motion and flattening of the lumbosacral area Laboratory studies failed to reveal anemia liver disturbances or gastrointestinal parasites Stomach x rays showed a deformity of the duodenal cap with a questionable niche A barium enema study revealed loss of normal haustrations of the colon in the distal half with an edematous mucosal pattern throughout Sigmoidoscopy showed the mucosa to be friable but without ulcerations

ACTH was begun 20 mg every 6 hours for 48 hours followed by 10 mg every 6 hours for 18 days There was definite improvement in the ulcerative colitis and spondylitis Without the patient s knowledge ACTH dosage was decreased to 20 mg daily There was im

(3) G troe t l gy 18 438 442 J ly 1951

omitted and the quantity reduced to 30 cc every hour Soft solid foods are added after stools reveal no occult blood. Medication consists of sodium phenobarbital 0 03 Gm every four hours atropine 0 6 mg four times daily and vitamins C K and B

Failure to respond to medical management particularly to transfusions is a definite indication for surgery In general operation is indicated if (1) patient in shock fails to respond to 1 500 cc whole blood (operation should be performed as soon as circulation can be stabilized) (2) patient responds to transfusion but more than 500 cc whole blood is required to maintain circulation (3) slow bleeding persists after several days of treatment indicating cancer rather than ulcer Hematemesis persistent severe pain syncope or recurrent bleeding during treatment demands utmost vigilance though operation is not mandatory The effect of age accuracy of diagnosis location of ulcer and any complicating disease must be carefully weighed in each case by both surgeon and internist

RESULTS IN TREATMENT OF BLEEDING GASTRIC OR DUODENAL ULCER

Classification	Jan 1940 Dec 1945		Jan 1946 July 1950	
	Cases	Deaths	Cases	Deaths†
Moderate				
Hematocrit 30 35				
Shock minimal	38	0	39	0
Severe compensated				
Hematocrit below 30				
Shock minimal	56	2	46	0
Severe uncompensated				
Hematocrit below 30				
Shock severe (1 000-1 500 cc blood daily needed)	14	0	31	1
Exsanguinating				
Hematocrit below 30				
Shock severe (poor response to transfusions)	9	7	7	1
Totals	117	9(7 6%)	123	2(1 6%)

* Six medical deaths 3 emergency operations with 2 deaths
† O medical death 9 emergency operations with 1 death

Results in 240 cases are given in the table In the most severe categories mortality of 30% in 23 cases in 1940-45 was reduced to 5 2% of 38 cases in 1946-50

[The preceding articles dealing with hemorrhage from chronic peptic ulcer are only a few of the many being written on this subject. It is apparent that from the welter of past controversy and confusion certain

sweetening flavoring or coloring agents and as flour improvers and bleachers

Two of four sweetening agents which have been or are now in use have proved too toxic for human consumption Dulcin (paraphenotolurea) after 50 years of use as a sweetening agent was shown harmful by chronic toxicity tests on animals Recent tests have shown that P4000 produces thyroid gland pigment changes and kidney damage Under the same experimental conditions saccharin and sodium cyclohexylsulfamate were apparently harmless Since discovery of the carcinogenic action of polycyclic aromatic hydrocarbons and their simple derivatives the azo dyes (commonly used for coloring purposes) have been suspected as potential toxic agents The following dyes have been shown to be carcinogenic usually producing hepatomas in rats o amino azobenzene p dimethylamino azobenzene (butter yellow) p monomethylamino azobenzene p amino azobenzene 2 2′ azonaphthalene 1 1 azonaphthalene and benzene azo naphthol (oil orange E) Although worldwide incidence of primary liver cancer does not point to azo dyes as directly causative of the disease in man it is only practical to exclude them from the human diet Other dyes should also be tested on animals before rather than after adoption for human consumption

The bleaching of flour is claimed to be due directly to consumer preference for white rather than colored bread the same claim is made for use of low extraction flour Although direct and indirect harm of bleaching have not been established removal of the germ and aleurone layers undoubtedly lowers nutritive value Flour improvers lighten the loaf by allowing incorporation of more air and gas thus reducing sustenance and nutritional value per unit volume Since discovery that agenized flour (treated with NCl_3) causes hysteria or running fits in dogs use of agene as an improver has been banned in the United States On the agenized flour analogy whereas NCl_3 destroys some or much of the methionine of gluten in developing toxic methionine sulfoximine it is possible that other improvers and bleachers destroy or modify one or more of the essential amino acids of flour protein making them physiologically unavailable Among chemical emulsifiers substituted for natural fat in food only lecithin and the mono and di glycerides of fat forming fatty acids

mediate exacerbation of symptoms and sigmoidoscopy showed inflammatory changes A course of cortisone (150 mg daily for nine days and 250 mg daily for six days) was given followed by 440 mg ACTH in eight days There was improvement until the eighth day of ACTH therapy when he complained of dull epigastric distress and vague generalized gas pains This was slightly relieved by food but the next morning he had persistent abdominal pain which became localized in the upper midabdomen with some radiation around the left costal margin and into the right lower quadrant No nausea or vomiting occurred but appetite disappeared and he felt weak Pain was controlled by ½ gr codeine Temperature was 100 F pulse rate 90 Moderate tenderness and slight rebound tenderness were noted in the epigastrium and right half of the abdomen Peristalsis was diminished and abdominal distention developed White cell count was 18 000 with 82 per cent in the neutrophilic series Red cell count was 3 500 000 Abdominal x rays showed gas filled intestinal loops but no free air Serum amylase value was 112 units Appendicitis was diagnosed Exploration 18 hours after onset of definite pain revealed a duodenal perforation It was repaired and five months later he had not had a recurrence and was considered cured

Activation of duodenal ulcer in this case may have been due to a great increase in gastric pepsin secretion and uropepsin excretion as a result of ACTH therapy Thus it appears that ACTH should be used with caution or not at all in patients with a history of peptic ulcer

Chemical Manipulation of Food Whereas great progress has been made in prevention and control of disease since 1900 such conditions as gastric and duodenal ulcer cholecystitis and appendicitis hypertension the leukemias disseminated sclerosis and diabetes have all either increased or remained etiologically obscure As some of these are most prevalent in the highly developed Western countries errors of living introduced or highly enhanced in modern times may be responsible Edward Mellanby[4] believes that chemical manipulation of food may possibly cause some of the errors Two aspects of current food processing and production methods which affect the consumer are (1) the possibility that substances conferring toxic properties are introduced into food and (2) the lowering of nutritional qualities of food by abstraction or reduction of important constituents or by dilution of nutritional constituents by air and water Unnatural chemicals may be added as sparers or extenders of fat or other foods as emulsifying aids preservatives antioxidants

(4) B M J 2 863 869 Oct 13 1951

or subsequent to hypoglycemia constitutes an index of the presence of vagus function

Afferent Loop Studies after Subtotal Gastric Resection. Because intestinal complications resulting from subtotal gastric resection for peptic ulcer often present difficult diagnostic problems Stanley H Lorber and Harry Shay[6] (Temple Univ) devised a special intubation technic whereby more comprehensive x ray study can be made

METHOD —A 5 cm balloon was tied over a bucket and fit into the smaller lumen of a Miller Abbott tube holes were made in the larger lumen proximal to the bucket Under fluoroscopic observation the tube was introduced 3 6 in into the efferent jejunal loop and the balloon slowly inflated with 50 100 cc air to block the efferent loop The patient erect was given 30 cc barium mixture If jejunal block by the balloon was complete he was then given 240 cc barium To fill the duodenal segment completely the patient was positioned variously on the fluoroscopic table Visualization was usually best in the right oblique position In some patients filling was complete only after they were allowed to sit in a chair for 5 10 minutes Occasionally the first swallow of barium passed through the efferent segment and revealed the tube in the afferent loop The balloon was then deflated and barium instilled by syringe through the other lumen directly into the afferent loop

Asymptomatic control subjects were studied after subtotal gastric resection Observation of stomal and duodenal stump areas helped to determine the amount of distortion from the surgical procedure In one the stump was irregular while in the others it was dome shaped or conical In two patients the stomal area was distorted A false pouch visualized in one was easily differentiated from ulcer because of its changing contour In another large folds in no way resembling niches produced by peptic ulcer were seen on all sides of the stoma

Four patients had troublesome digestive symptoms after subtotal resection Routine studies including a complete gastrointestinal series were normal Stump ulcer was found in a patient after subtotal resection without removal of the pylorus Symptoms one year later were similar to those before operation except that the pain had shifted from the epigastrium to the right upper quadrant Routine x ray studies revealed no abnormalities X ray intubation studies (Fig 93) suggested reactivation of an excluded duodenal ulcer with

(6) Am J M S 2 2 544 53 N mbe 1951

are recommended for use in such a staple dietary product as bread Polyoxyethylene stearate sorbitan esters of fatty acids polyoxyethylene sorbitan esters of fatty acids and the glycerides of acetylated tartaric acid are specifically excluded

Studies on Vagotomy in Treatment of Peptic Ulcer Two fundamental questions are yet to be answered before final evaluation of vagus section can be attempted (1) the proportion of patients who continue to have unpleasant symptoms or recurrence of ulcer symptoms after several years and (2) whether the pronounced decrease in gastric secretion and motility found in the early postoperative period is permanent or not

Results of physiologic studies of 50 patients by I F Stein Jr and Karl A Meyer[5] (Chicago) demonstrated three types of response on the basis of vagus function which have been termed (1) normal vagus function (2) partial vagus function and (3) no vagus function No significant change in the gastric secretory or motor activity is present in patients with normal vagus function following surgery A striking reduction in motility and in both spontaneous and stimulated acid secretion of the stomach is demonstrated in patients with partial vagus function and those with no vagus function three to four years after vagotomy This reduction is greatest in patients with no vagus function No evidence of any return of gastric activity is present in this group Slight return of acidity is found in patients with partial vagus function as determined by the basal secretion however there is still a decided decrease compared with the preoperative level

The previous failure to recognize the existence of the intermediate group (partial vagus function) probably accounts for reports of a lack of correlation between the physiologic and therapeutic effects of vagotomy Response of patients with partial vagus function to insulin hypoglycemia is characteristically delayed and may be missed unless the test is continued for at least 2½ hours after the injection of insulin The appearance of a spontaneous secretion of free hydrochloric acid during periods of night or basal secretion after vagotomy indicates the presence of vagus function In addition the appearance of vagal type motility either spontaneous

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(5) Surg Gyne & Obst 93 5 635 November 1951

Experimental Study of 79 Cases Showing Early Postgastrectomy Syndrome after the Polya type operation was conducted by T J Butler and W M Capper[7] (Bristol Royal Hosp) 95 postoperative patients without syndrome served as controls Symptoms occurring within the first half hour after a meal and their relative frequency are shown in the table An attempt was made to reproduce these symptoms to identify their cause

Balloon distention of the jejunum was accomplished in 26 patients with the early syndrome and 23 controls All air

SYMPTOMS IN 79 CASES	
Epigastric fulness and distress	79
Pallor	76
Sensation of warmth	72
Nausea	64
Palpitations	50
Vomiting of bile stained fluid	41
Eructations	9
Borborygmi	8
Vomiting of food	5
Sensation of cold	3

was aspirated from the balloon which was usually situated about 12 in beyond the anastomosis in the efferent loop of jejunum then 80 100 and 120 ml water was injected at half hour intervals aspirating fully after each injection Experiments were performed in the fasting patient in the supine and then in the erect position Jejunal distention produced a sensation of fulness referred to the umbilicus this was independent of posture Vasomotor symptoms developed in only two patients one from each group Sympathetic splanchnic block abolished the sensation of fulness produced by distention in 85% of patients with the syndrome and in 69% of controls

Radiologic studies were performed in both the supine and erect positions in 167 patients without syndrome (*72 Billroth I and 95 Polya operations*) and in 61 with syndrome after the Polya operation There was no significant difference in incidence of rapid emptying delayed emptying and afferent loop filling between patients with and those without the early postgastrectomy syndrome On occlusion of the stoma *24%* of Billroth I patients had feelings of distention but none had vasomotor symptoms accumulation of barium in the stomach produced feelings of distention in about one third without

(7) B M J 1 1177 1181 May 26 1951

cited in the literature is a bitter taste in the mouth (J.A.M.A. 148 87 1952) which may be constant or chiefly nocturnal The sensation is a disagreeable and disturbing one The chewing of gum is usually an effective means of relief —Ed.]

Premalignant Lesions of Gastrointestinal Tract I Significance of Roentgenologic Evidence of Hypertrophic Gastritis According to Robert P Barden[9] (Univ of Pennsylvania) chronic hypertrophic gastritis and gastric carcinoma may be indistinguishable by roentgen examination In both appearance of the stomach is highly abnormal

Case 1 —Man 55 had dyspepsia and epigastric pain for several years which was only temporarily relieved by diet There was no vomiting bleeding or significant weight loss Physical and laboratory examinations were negative Roentgen examination disclosed striking changes in the mucous membrane of the stomach with irregular giant rugae in the lower third After carcinoma was diagnosed partial gastric resection was performed Examination of the specimen showed extensive hypertrophic gastritis without evidence of neoplasm

Case 2 —Man 51 had weight loss anorexia epigastric pain and occasional vomiting for a year Stools were tarry Physical examination revealed an indefinite mass in the upper midabdomen Hemoglobin value was 37% Roentgen study showed great distortion and enlargement of the rugae in the lower half of the stomach Subtotal gastric resection was done after carcinoma was diagnosed The liver and lymph nodes appeared free from disease The specimen showed extensive carcinoma infiltrating the mucosa and submucosa up to the line of resection Microscopy showed multiple foci of carcinoma apparently arising independently with diffuse gastritis and cellular metaplasia throughout the mucosa

The premalignant character of chronic hypertrophic gastritis is suggested by the histories of two patients with similar symptoms and roentgen diagnosis of gastritis One was operated on after six months of symptoms and had gastritis only whereas the other was operated on after two years of symptoms and had gastritis and carcinoma In two patients who were under careful medical supervision for a long time repeated roentgen studies demonstrated definite organic disease in the stomach Either when the patients were first seen or while they were under observation carcinoma was present Because roentgen changes were identical with those of hypertrophic gastritis correct diagnosis was not made until too late There was no way in which the lives of these patients could have been saved unless gastric resection had been done when chronic hypertrophic gastritis was first diagnosed

(8) Am. J Roentg ol. 66 915 921 December 1951

symptoms in the Polya series In those with syndrome 79% had symptoms during examination in the erect position occurring while barium was still in the stomach in 25% Patients complained of fulness in the epigastrium increased pulse rate sweating two fainted In all three groups change from the supine to the erect position caused descent of the stoma greater in patients with early syndrome than in those without symptoms This is attributed to stretching of the gastric remnant by weight of its contents There was no difference in the blood sugar curve of those with and without the early syndrome

The effect of a mercury loaded bag in the gastric remnant was investigated in the 61 patients with early syndrome With the patient supine an amount of mercury corresponding to the weight of the meal which normally produced symptoms was introduced and the patient then assumed the erect position In 49 patients (80%) there were no symptoms in the supine position 12 noted some heaviness in the epigastrium only On assuming the erect position 57 patients (93%) had heaviness and fulness in the epigastrium associated with nausea increased pulse rate pallor and sweating 24 had palpitations and a feeling of suffocation 2 fainted On return to the supine position symptoms disappeared in 5 10 minutes When the test was repeated after the patients had been in the supine position for one half hour only 10 had symptoms as before 4 had heaviness in the epigastrium only the other 45 had no symptoms until 2 7 oz additional mercury was added to the bag Splanchnic block removed symptoms in 41 (77 3%) of the 53 patients in whom it was performed

It is concluded that several different mechanisms are involved in production of the early postgastrectomy syndrome jejunal distention producing a sensation of fulness and drag produced by the combined weight of the gastric and afferent loop contents in the erect posture leading to vasomotor effects Abolition of the effect of gravity relieves the latter but not the former Splanchnic block suggests that the syndrome is mediated by the sympathetic rather than the vagus nerves

[Research directed to the cause prevention or more effective treatment of a not uncommon postoperative disorder is welcome This one upsets some former concepts of etiology and advances new ones Fortunately the syndrome is only of significant degree in about 15% of patients and in most the disturbances are resolved sooner or later One symptom rarely

In the malignant group 54% of patients died with extensive metastatic spread Hemorrhage (12%) and perforation (9%) were relatively less common thus constituting criteria of differential significance Only 11% of benign and 38% of malignant ulcers were correctly diagnosed before autopsy The nature of the hospital a large municipal institution to which many emergency cases are brought accounts for the high per cent of acutely ill patients with little previous history and the lack of time for diagnostic evaluation

This study serves to re emphasize the fallibility of absolute *dependence on any clinical feature in differential diagnosis* of benign and malignant gastric ulcers The proper diagnosis when possible can be made only through use of many clinical data each of which is of uncertain significance but whose combined value may permit a reasonably accurate decision

[The last statement is an intriguing one for which there is much justification In contrast to the contention of some surgeons that there is at least a 35% error in distinguishing a benign from a malignant ulcerating *gastric lesion is the recent opinion of several authorities* that such error should not exceed 6% provided all symptoms and signs together with the effect of adequate medical treatment in doubtful cases are properly evaluated by those with specialized skill —Ed]

Mortality and Survival in Cancer of Stomach Statistical Summary of Experience of Mayo Clinic covering the period 1907-49 is presented by Joseph Berkson Waltman Walters Howard K Gray and James T Priestley[1] Figure 94 shows the number of males and females in specific age groups by decades The outstanding fact demonstrated is the preponderance of males ratio of males to females was 3 4 1 and the preponderance was shown at all ages Of 9 620 operations 47 8% *were resections 13 8% palliative operations and 38 4%* exploratory laparotomies with respective average hospital mortality rates of 13 3 12 3 and 3 8% All hospital deaths were included regardless of cause The risk was higher in older than in younger patients being manyfold greater in the decade 60 69 than in 30 39 At all ages except 70 79 females showed a smaller hospital mortality rate than males Before 1938 average mortality for the patients who had undergone resection was 16 2% but there was striking variation in the calculated rates during this period Since 1937 there has been a definite decline in mortality with stabilization at about 8%

(1) P oc Staff M et M y Cl 27 137 151 Ap 9 1952

With the present limitations in understanding with regard to adequate diagnosis and treatment of gastric carcinoma a different and perhaps more radical approach to the problem seems inescapable Since in an unpredictable number of patients with hypertrophic gastritis of several years duration carcinoma will develop prophylactic use of gastrectomy should be considered in all such cases

Anatomic Study of Benign and Malignant Gastric Ulcerations was undertaken by R P Boudreau J P Harvey Jr and S L Robbins[9] to assess the validity of established diagnostic criteria Among 8 493 autopsies performed at Boston City Hospital in 1940 49 234 cases of gastric ulceration were found in patients aged 50 or over 168 were benign and 66 were malignant lesions Incidence of both types rose with advancing age When data were corrected for the number of autopsies performed in each decade benign ulcers were found to occur in about the same ratio through the three decades after 50 whereas malignant ulcers showed a slight but progressive rise in incidence Like age size of the ulcer crater proved of limited diagnostic value Although considerable emphasis has been placed on the differential importance of the 4 cm crater about 50% of malignant ulcers were less than 4 cm in diameter and 10 5% of benign ulcers were over 4 cm Among all lesions over 4 cm in diameter 62% were malignant and 38 benign This per cent distribution is undoubtedly high due to exclusion of all surgical material No area of the stomach was immune to malignancy carcinomatous lesions occurring in all in sufficient numbers to warrant confusion with benign ulcers in the same area Over half (58%) of benign and 56% of malignant ulcers were found in the prepyloric region In all two thirds of lesions in the prepyloric area and 51% of those on the greater curvature were benign On the lesser curve 29% of ulcers were malignant

Two important complications of gastric ulceration are hemorrhage and perforation Although perforation was noted almost as often in benign ulcers (18%) as in malignant ones (12%) significant hemorrhage was commoner in the former being found in 37% as compared to 27% These complications were the first and third most frequent causes of death in the benign group together being responsible for 43% of fatalities

(9) J A M A 147 374 3 7 Sept 9 1951

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(9) J A M A 147 374 3 7 Sept 9 1951

during the five years after operation If the 56 patients found not resectable had come to the surgeon earlier then without any improvement in the pre ent surgical results there would have been 18 more survivors

[From the standpoint of the internist general practitioner and lay man the pessimism r garding gastric cancer which has prevailed is now less justified Progress has been made and encouraging reports come from many institutions This study reveals that the exploratory laparot omy rate has increased 33% the resectability rate about 50% and the five year survival rate about 200% (from 5 to 14% over the years) At the same time mortality rate for resection has dropped from 16 to 8% The various factors which have made possible the reduced mortality are generally known Fifty per cent of patients who had partial gastrectomy and were without discern ble metasta es lived five year Thus the crux of the problem is in g tting more patients to the surgeon while the growth is re ectable and before the a lvent of metastases

There is much room for improvement even with due allowance for the insidiou nature of the di ea e Routine fluoro copy gastroscopy cytologic examination of gastric content earlie and more frequent resort to opera tion on all suspicious mall ulcerating lesions cancer detection clinics and the close observation of pat ents with precursor of cancer ha helped impro e the picture A dependable biologic test for cancer would be defin tely superior to mo t existing diagno tic t chnics —Ed]

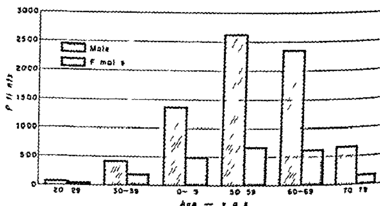
THE BILIARY TRACT LIVER AND PANCREAS

Acute Cholecystitis In a 15 year survey Robert W Bux ton Dean K Kay and Frederick A Coller[2] (Univ of Michi gan) reviewed 338 cases diagnosed as acute cholecystitis and selected 109 with histologic confirmation for further study During this study 42 patients had cholecystectomy explo ration of the common and hepatic ducts of 9 disclosed stones in 4 Death of five patients does not indicate current operative hazard all might have survived with better pre and post operative management including liberal use of antibiotics Simple drainage of the gallbladder was performed on 31 pa tients Three died (9 6%) Two might have survived with present day care Of 36 patients treated with bed rest sedation parenteral fluids gastric suction and later antibiotics 3 died 2 of perforation and 1 of necrotizing cholecystitis and lung abscess Over all mortality of 10 1% contrasts sharply with the low death rates reported by others usually attributed to early cholecystectomy In this series the trend away from emergency cholecystectomy greatly improved patient survival

(2) J A M A 146 301 307 May 6 1951

Of all patients who underwent resection an estimated 31 6% were living 5 years after operation 23 2% 10 years after operation 17 2% 15 years after operation 12 2% 20 years after operation Almost all the patients who underwent palliative operations and those who underwent exploration only had died when five years had elapsed In the statistics on survival 168 patients with sarcoma or lymphosarcoma were excluded

Of 4 429 patients who underwent resection 58 9% had metastases Five year survival rate for the group without



F g 94—Age d t but o by x of pat e ts who u d w t pe ati for c n f t ma h (Cou t y f B k n J f f P oc. Staff M t Mayo Clin 27 137 151 Ap 9 195)

metastasis was 48 5% whereas for those with metastasis it was 18 6% 10 year rates were 36 9 and 12 8% respectively Broders grading of malignancies showed unequivocal relationship to survival The lower the free gastric acidity at the time of operation the poorer the outlook Whether this was etiologic —i e whether low gastric acidity is a precursor of gastric malignancy—or whether the low acidity resulted from invasion of the acid forming cells was unknown but correlation between low gastric acidity and poor prognosis was clear

In 1940–49 of 100 patients with gastric malignancy 14 survived Of the 86 who died 20 were judged inoperable on physical examination 36 had a lesion found not to be resectable at laparotomy 4 died in the hospital and 26 died

surgery jaundice spontaneously cleared and apparently did not recur the others were operated on after jaundice had subsided Stones were found in 4 of 11 patients with a dilated common duct a 9 3% incidence of proved stones in the entire jaundiced group It would therefore appear that jaundice in acute cholecystitis may often be due to hepatitis rather than common duct obstruction This view is further supported by

CRITERIA FOR DIAGNOSIS OF ACUTE CHOLECYSTITIS IN 85 NONOPERATIVE CASES

Basis of Diagnosis	No. Cases
Typical pain	85
Right upper quadrant tenderness	83
Right upper quadrant muscle spasm	62
Palpable gallbladder	43
Fever over 100 F	84
Leukocytosis	71

the elevated cephalin flocculation reaction found in one third of jaundiced patients as compared to 3% of the nonjaundiced Of 33 patients operated on when all clinical evidence of acute cholecystitis was believed past only 21% had operative and histologic evidence of quiescence The interval between onset and operation ranged from under 3 weeks to over 2 months patients had been afebrile 8 79 days The persistence of the acute symptoms suggests little possible gain in the first three months from postponement of surgery in the hope that edema and inflammation will subside and technically facilitate cholecystectomy

Nine patients (6 4%) in this series died four among those operated on and five among those not operated on Most patients (71%) gave histories of previous gallbladder disease indicating that much of acute cholecystitis could be eliminated by cholecystectomy before acute attack Five of the dead had had gallbladder disease six months to many years before onset of acute symptom Of all 140 patients 21 4% were not hospitalized until one week or more after the onset of acute cholecystitis delay was a factor in three deaths Surgery within 48 hours of hospitalization might have saved two patients reducing mortality rate to 5% However the potential margin of improvement is so small that it might well be offset by higher operative mortality in older poor risk patients These findings emphasize the need for individualized approach to treatment

due possibly to better diagnosis and medical management and to prompt surgical intervention when the patient failed to improve

The decision to remove or to drain the acutely inflamed gallbladder should be based on (1) the patient's tolerance for a general anesthetic and the trauma accompanying cholecystectomy and possibly choledochostomy and (2) the hazard of accidental damage to the biliary ducts in adjacent surgery when the normal anatomic picture is obscure Cholecystostomy is preferable because it obviates these complications and can be used for the seriously ill under local anesthesia If surgery is not obligatory and a diagnosis of acute cholecystitis is the only indication the following specific indications should be considered (1) failure of rapid and prompt regression of fever leukocytosis and abdominal signs of acute inflammation under adequate and vigorous medical management (2) diabetes (3) severe cardiac and renal disease (4) pregnancy (5) exacerbation of concomitant diseases (6) recurrent acute cholecystitis (7) unremitting jaundice In the absence of jaundice cholecystectomy may be desirable particularly with acute disease of short duration With jaundice and acute inflammation calculus obstruction of the biliary ducts is difficult to verify except by surgical exploration or cholangiography After cholecystostomy the latter is easier and less hazardous

In this study 58% of patients seen and treated within two days of onset and 42% seen within three to five days survived without operation Only 1 of 21 patients seen five or more days after onset got well without surgery Thirty one patients had interval cholecystectomy 19 of them after cholecystostomy 1 died of postoperative hemorrhage due probably to vitamin K deficiency Of 35 patients treated either medically or by cholecystostomy 28 were living and 14 had varying degrees of recurring gallbladder symptoms

Acute Cholecystitis Study of 140 Cases is presented by Robert Freund[3] (State Univ of New York Brooklyn) In instances diagnosis was based on operative and pathologic findings or autopsy and in 85 on four or more of the criteria listed in the table Clinical jaundice or an icteric index of 15 or more was found in 30% of patients Although half had no

(3) Am J Surg 82 03 08 December 1951

roentgenograms In both the sphincters of Oddi were cut through their superior borders The incision was extended until the lumen of the sphincter was adequate to draw a no 16 F long arm T tube into the duodenum easily Length of the incision varied from 1 to almost 2 cm Biopsy specimens taken at sphincterotomy showed increased fibrous connective tissue in the sphincter muscle with considerable increase in over all thickness Both gallbladders were removed despite



F g 95 (l ft) —E n type f al h lecy t g m how g dilated common d t d g ab pt tap w h n dy d od m
F g 96 (ght) —Op t l l g og am
(Co te y f E t gt P P S g y 31 367 372 Ma ch 1952)

a normal appearance they were normal on microscopic examination

The three patients were relieved of the severe attacks of pain in the right upper quadrant Only one was asymptomatic however and the follow up period was short (longest 18 months) One patient was troubled with abdominal discomfort related to a small incisional hernia Another was later hospitalized for burning epigastric distress which was relieved by food or amphojel® On discharge she was greatly improved symptomatically as a result of banthine® therapy In no patient were jaundice or acholic stools noted postoperatively All patients gained some weight

[Accumulating evidence emphasizes the necessity of routine scrutiny of the terminal portion of the common bile duct to detect contraction stenosis the result of spasm or fibrosis in absence of other demo

[Two representative temperate articles by surgeons on a subject of perennial interest on which some disagreement persists as to the urgency of immediate operation in all cases As in acute appendicitis the consensus favors early intervention granting correct diagnosis and no serious contra indications All facets of the problem from the standpoint of immediate and delayed operation were ably considered in discussion of the Buxton Coller paper —Ed]

Fibrotic Stenosis of Terminal Common Duct Philip F Partington[4] (Western Reserve Univ) discusses three patients with decided symptoms of biliary tract disease despite normal appearing gallbladders on standard cholecystography For several years they had had epigastric pain and sharp pain in the right upper quadrant which occasionally radiated to the back and was associated with nausea and vomiting In two patients typical attacks of pain could be produced with mor phine Since the symptoms could not be explained all three were considered psychoneurotic None had been jaundiced but weight loss up to 45 lb had occurred in two Laboratory data were not distinctive Icteric index serum amylase cephalin flocculation and thymol turbidity determinations were normal X ray examination of the intestinal tract was noncontributory Oral cholecystograms revealed gallbladders which filled emptied with some delay and contained no stones The com mon ducts were slightly dilated and terminated with abrupt narrowing near the sphincter of Oddi (Fig 95) In two pa tients antispasmodics did not affect this narrowing All three were considered to have partial obstruction of the terminal common duct near the sphincter of Oddi

At operation the gallbladder appeared grossly normal in two patients and was somewhat thickened in the third In all three operative cholangiograms confirmed the preoperative diagnosis (Fig 96) In one because of partial relaxation of the sphincter of Oddi in response to amyl nitrite given preop eratively the common duct was drained and the gallbladder removed Microscopic examination of the gallbladder showed cholesterosis After three months of drainage by means of a T tube there was still pronounced narrowing near the sphinc ter of Oddi and pain was produced by clamping the T tube Transduodenal exploration was done On section the walls of the sphincter were firm grayish white and about 2 5 mm thick

The two other patients had duodenal scarring which sug gested inactive duodenal ulcers despite normal gastrointestinal

It is suggested that the variable clinical picture of hepatic coma is almost certainly of biochemical origin and may be directly related to the variable pattern of the blood amino acids

Recognition and Treatment of Hepatic Amebiasis in 28 patients at the University of Iowa Hospitals in 12 years are discussed by Donald C Zavala and Henry E Hamilton[6] Among helpful diagnostic aids were (1) tender often enlarged liver (2) fading suntan complexion (3) elevation or fixation of right leaf of the diaphragm (4) little or no change in liver function test results (5) positive complement fixation reaction with a fall in titer after specific amebacidal therapy and (6) specific therapeutic response Amebacidal drugs primarily effective against intestinal amebiasis are vioform* chiniofoim diodoquin* carbarsone milibis* and two new thioarsenite derivatives of carbarsone oxide Although aureomycin and terramycin have been favorably reported clinical trial is as yet inadequa e Chloroquine and emetine both specific for amebic hepatitis and abscess are effective against extraintestinal amebia is Chloroquine s high therapeutic effect and lack of toxicity make it superior to emetine it should always be given with a local amebacidal drug preferably diodoquin* Secondary infection should be treated with the appropriate antibiotic

Of 28 patients studied all but 2 had intestinal lesions and parasites in the stools 6 had liver abscesses 2 without diagnosis until autopsy received no specific treatment 15 received intermittent or alternating therapy with one of the iodides or emetine 11 had combined therapy with emetine and an iodide for 8 and chloroquine and diodoquin* for 3 The two untreated patients died of metastatic complications Three of those under intermittent or alternating therapy had relapses one with intestinal amebiasis returned in five months with a large liver abscess the other two each returned three times in less than three months with recurring bowel lesions The group treated with combined therapy had no relapses

Diagnosis of Hepatitis Viral hepatitis must be considered in all patients with jaundice and in many with conditions of acute onset without jaundice It can occur in any age group and in any geographic area With early diagnosis proper

(6) Ann Int M A 36 110 125 J y 19 2

disease especially calculi in the extrahepatic ducts Correct diagnosis of the condition giving rise to pain following cholecystectomy often is difficult and it is to be hoped that this newly recognized entity will contribute to the solution of some vexing problems —Ed]

Observations on Symptomatology and Pathogenesis of Hepatic Coma. *J M Walshe*[5] (University College Hosp London) discussed 18 cases Acute liver failure (acute yellow atrophy) was present in 12 patients long standing cirrhosis in 4 obstructive jaundice due to bile duct carcinoma and liver metastases in 1 and the Budd Chiari syndrome in 1

The neurologic symptoms and signs indicated wide disturbances of cortical function involvement of pyramidal tract and basal ganglions The full picture consisted of personality changes mania and coma with dilated pupils choreiform movements of the arms tonic grasping and sometimes lead pipe or cogwheel rigidity absent abdominal reflexes increased knee jerks ankle clonus and extensor plantar responses In some patients there was either spasticity or lead pipe rigidity of the legs During the early phase of coma patients sometimes adopted a characteristic posture with the legs tightly drawn up to the abdominal wall Cranial nerve palsies were rare and convulsions were not observed All these changes were more prominent in children than in adults

A number of theories to account for such changes have been advanced Hypoglycemia may precipitate convulsions but is not otherwise directly associated with the production of symptoms The possibility of an intestinal toxin passing through a damaged liver to enter the general circulation is discarded as is the theory that acetylcholine accumulates in the blood as a result of a fall in the plasma cholinesterase Experimental work has suggested that the products of autolysis of the liver parenchyma which have a high amino acid content are toxic It is possible that these products entering the circulation account for the phase of excitement observed in acute liver failure The disturbed pattern of blood amino acids which results from both acute and chronic liver failure may be toxic to the brain In some cases interference in utilization of glutamic acid may occur with consequent breakdown in the ammonia binding mechanism of the brain There may also be disturbance of carbohydrate utilization leading to disturbances of consciousness and reflex changes

(5) Quart J Med 0 421 438 October 1951

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(6) Ann Int Med. 36 110 125 Ja y 1952

therapy can be initiated and surgery and other procedures of potential harm to the liver avoided Presenting symptoms and signs vary according to the stage of disease diagnosis depends



F g 97 —L cut h p t t × 110 Sт me tak fi lays lt r set f ja d Ch r t m l a hlt t w th t n to n o d I hymal l ll g t w th g la t g d b cl te cells d t (Co t f Sbo V M d K ll T C G t oe te logy 19 4 4 440 N ember 1951)

on knowledge of the characteristic features of hepatitis at the time the patient seeks medical advice

Victor M Sborov and Theodore C Keller[7] analyzed 221 cases of hepatitis in 156 acute cases diagnosis was made by subsequent course or liver biopsy in 48 chronic cases by liver biopsy in 17 cases with extrahepatic biliary obstruction by

(7) Gast oenterol gy 19 4 4 440 N mbe 1951

laparotomy About 80% of the acute group had a prodromal stage characterized by anorexia nausea vomiting malaise and fatigue dark urine epigastric distress abdominal distention and discomfort in the right upper quadrant Physical examination was often normal and laboratory data nonspecific About 20% of patient had no prodromal stage in these jaundice and dark urine were the first definite evidences of disease The liver was usually enlarged at this stage and very tender pain sometimes persisting for several hours after palpation

HEPATIC ENLARGEMENT 56%
RUQ ACHE %
EASY FATIGABILITY %
HEPATIC TENDERNESS 37%
SPIDER ANGIOMATA 3 %
INTERMITTENT NAUSEA 29%
EPIGASTRIC DISTRESS 2 %
NERVOUSNESS 2%
INTERMITTENT MALAISE %
INTERMITTENT DIARRHEA %
PALMAR ERYTHEMA %
FATTY FOOD DYSCRASIA 0%
PALPABLE SPLEEN %

Fig 98—Sy pt m a d n 48 se of hr al hepat t s. (Courte y f Sh o V M d Kell 1 C G t oe t r l gy 19 424 440 N embe 1951)

The test for urine urobilinogen has special diagnostic value since it shows a higher percentage of positive results in all stages of jaundice when the serum bilirubin levels are under 5 mg/100 cc whereas other tests of parenchymatous liver involvement tend to show a smaller number of positive results than in more deeply jaundiced patients Liver biopsy is indicated in all patients who do not show a sufficiently characteristic clinical and laboratory picture to establish a diagnosis Among patients with acute hepatitis 46 biopsies were performed 2-45 days after onset of jaundice The characteristic picture of early disease is shown in Figure 97 Biopsy specimens taken in later stages showed changes varying only in degree

Chronic hepatitis should be considered in diagnosis of an obscure gastrointestinal condition with associated fatigue and

therapy can be initiated and surgery and other procedures of potential harm to the liver avoided. Presenting symptoms and signs vary according to the stage of disease; diagnosis depends



Fg 97—I cut h p t t × 110 Spe m n tak fi day ft o t f j d Ch t t m l hlt t w th xt n nto s d I h l l ll g t w th g l r t g d b l ate cells d t (C t f Sl V M d K ll T C G t t ol gy 19 4 4 440 N mbe 1951)

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tests which gave positive results most often were the urine urobilinogen bromsulfalein and zinc turbidity in that order The histology in these cases had many features in common with that seen in the later stages of acute hepatitis (Fig 99) Changes not characteristic of acute hepatitis included slight to great increase in portal connective tissue extension of the portal canal into adjacent lobules and increased number of bile ducts Although some cases of chronic hepatitis may progress to the stage of hepatic cirrhosis outcome in most is not known Therefore recognition of this entity is important not only because of possible therapeutic indications but also because these patients should be observed over a long period to determine if the disease process is going to progress

[Viral hepatitis continues to be an important problem in both the military and civilian population and timely diagnosis of sporadic cases still present difficulties These studies were carried out in an Army hospital designated as a diagnostic and therapeutic center for hepatic diseases — Ed]

Jaundice in Chronic Hepatitis (Cirrhosis of Liver) William E Ricketts[8] (Univ of Chicago) reports data on 28 consecutive cases of cirrhosis of the liver with marked jaundice (total serum bilirubin above 5 mg/100 cc) Simultaneous clinical and histologic observations and conventional biochemical determinations were carried out The ages of the patients 22 of whom were males covered a wide range A history of alcoholism was obtained in 23 cases and onset of symptoms was insidious in 21 The presence of one or more of the following findings helped establish the diagnosis collateral circulation of the abdomen spider nevi telangiectasia hard or nodular liver and varicose veins of the esophagus Punch liver biopsy was the most important single diagnostic process used since it served to demonstrate both liver fibrosis and changes in the liver parenchyma (Fig 100) Such biopsies were done in 17 cases and repeated in 8 Specimens for histologic study were obtained at surgery in two cases and at autopsy in nine

Jaundice in cases of cirrhosis represents active parenchymatous liver disease in contrast with asymptomatic nonjaundice cases in which necrobiosis of liver cells areas of recent necrosis and bile stasis are absent In 22 of the 28 cases there were diffuse degenerative changes in the parenchyma with a

(8) G t oe t l gy 17 523 534 Ap l 1951

disability which follows a bout of acute viral hepatitis by months or years Whenever a patient has residual symptoms clinical or laboratory signs of hepatic dysfunction which persist or recur intermittently six or more months after onset of



Fg 99—L h n h p t t X 110 Spe m n tak n 13 m th ft o t of j nd N t m ll f cal gg gat f m o lea ll pe t g n lob l (C te y f Sbo V M d K lle T C G st oe t l gy 19 424 440 N mbe 1951)

acute hepatitis chronic viral hepatitis may be diagnosed In addition all such patients should show histologic abnormalities at liver biopsy These criteria were met by the 48 patients in this series Average time from onset of acute hepatitis to the present hospitalization was 30 months (range 6 96) The clinical picture is summarized in Figure 98 The liver function

all cases of parenchymatous liver disease avoidance of further liver injury by toxins promotion of regeneration by dietary methods and lipotrophic substances and improvement of general nutrition If ascites and edema are present the tendency to water and salt retention must be corrected Bed rest is imperative and hospitalization is usually required Although enteral protein replacement is preferable parenteral therapy with salt poor albumin or plasma is indicated in cases of collapse shock after hemorrhage or marked oliguria

Pain in Acute and Chronic Diseases of Liver is an important and useful symptom but one which is poorly understood due to incomplete knowledge of the nerve supply of this organ According to Howard P Lewis[9] (Univ of Oregon) studies of innervation indicate that the liver is supplied by sympathetic fibers arising from the seventh to the tenth thoracic nerves bilaterally right and left vagus and in some persons by branches of the right phrenic nerve These after giving off fibers to the undersurface of the diaphragm mingle with fibers of the diaphragmatic plexus Phrenic fibers from this plexus supply the coronary and falciform ligaments and probably part of the adjacent liver capsule Other phrenic fibers continue onward pass through or near the phrenic ganglion and enter the hepatic plexus from which they appear to be distributed to the gallbladder and cystic duct in the liver where they accompany the visceral nerves

The characteristics of pain in hepatitis cirrhosis carcinoma of the liver and liver abscess are often sufficiently striking to aid both diagnosis and prognosis Abdominal pain is common in the preicteric stage of hepatitis in the form of a dull ache or dragging sensation of the epigastrium or upper right part of the abdomen In some patients with acute onset pain may be so severe or unusually located as to suggest acute appendicitis cholecystitis perforated viscus or when intermittent and colicky gallstone colic In the absence of an enlarged or tender liver bilirubinuria is a helpful clue as are the systemic manifestations In addition fist percussion over the liver often causes pain which typically appears after a latent period of several seconds and gradually increases in severity often persisting for some time afterward Pain is occasionally first apparent with onset of icterus or if present

(9) A I L M 4 33 8 8 888 Octobe 1951

variable degree of liver fibrosis The liver cell cytoplasm appeared irregular with a coarse hyaline network There were no hyaline and fatty degenerative changes in the other six cases In three there appeared to be broad bands of connective tissue separating large areas of parenchyma These changes suggested an initial necrosis of liver tissue followed by scarring However active *parenchymatous changes* of varying degree were present in all There was no relation between

Fg 100—P h l b (y pe m f m ch alcoh l w th) d c show g hy l l g nd p o u d f tty filt t on H matoxyli e ta n r d c d f om × 510 (C rt y of Ri k tts W E G t oente l gy 17 523 534 Ap l 1951)

jaundice and the degree or type of fibrosis Jaundice appeared as a slight transitory almost unnoticed episode in the course of chronic hepatitis or most commonly it was accompanied by other symptoms and signs of liver failure such as edema ascites and encephalopathy It was considered a serious sign contraindicating abdominal surgery

Adequate medical treatment is important since even patients with severe liver failure can recover clinically with disappearance of degenerative features regeneration of liver parenchyma and improvement in parenchymal function Principles of conservative management of jaundice are similar in

the surface Steady pain over the liver local tenderness chills fever and mild gastrointestinal symptoms characterize a solitary abscess Multiple abscesses and pylephlebitis tend to have a milder diffuse pain and tenderness and a higher and more septic type of fever with multiple severe chills and sweats Pain is present in about 75% of patients with amebic abscess is slower in onset and often less intense Localization follows the same general rules as in pyogenic abscess Shoulder pain is usually due to diaphragmatic irritation by an abscess in the dome of the liver Sudden thrust of the finger on the liver quick compression of the thoracic cage or a sharp mild blow over the liver may cause as in hepatitis and pyogenic abscess a deep aching pain that persists for a short time The symptoms and laboratory evidence of Endamoeba histolytica infestation are important in differential diagnosis

[A study of factors underlying the pain mechanism in parenchymatous disease of a solid viscus like the liver or pancreas for that matter deserves our respectful attention The literature of the past decade or two furnishes ample proof that pain of all degrees of severity may be prominent in acute viral and chronic hepatitis especially the former Pain in the liver area particularly in chronic nonicteric disorder heretofore too readily suggested the need for surgical intervention A reorientation of our attitude in the light of new knowledge should materially reduce the number of patients needlessly operated on under great risk Otherwise pain may not be the useful and important symptom of hepatic disease which Lew considers it —Ed]

Chronic Intrahepatic Cholangitis and Effect of Sulfonamides on Its Clinical Manifestations Chronic inflammation of the intrahepatic bile ducts leading to biliary cirrhosis is characterized clinically by long standing jaundice periodic febrile attacks and pronounced enlargement of liver and spleen Factors underlying its development are biliary stasis and infection which may reach the liver via the blood or duodenum The liver itself is large smooth and slightly granular with early profuse periportal cellular infiltration Later fibrous tissue proliferation increases and liver lobules become circumscribed by strands of connective tissue Medium and small bile canaliculi are surrounded and sometimes obliterated by dense connective tissue infiltration by polymorphonuclear leukocytes lymphocytes and plasma cells may occur No definite organism has been proved responsible for the intrahepatic infection although Streptococcus viridans has often been found in the bile M Rachmilewitz[1] (Hebrew Univ

(1) Gastroenterology 18 530 545 August, 1951

before becomes so intense as to suggest obstruction of the bile duct Upper abdominal rigidity may be pronounced and at this stage generalized steady or colicky abdominal pain may appear Pain in the right shoulder is noted occasionally possibly due to parenchymatous inflammation Aching sharp epigastric or right upper abdominal pain appearing in the erect position or with exercise during the convalescent phase of acute hepatitis usually indicates incomplete recovery and need for further bed rest Increased pain over the liver or in the epigastrium in an otherwise uncomplicated case of hepatitis may mark onset of acute hepatic necrosis or exacer bation of the disease The causes of pain in hepatitis include distention of the capsule reflex intestinal disturbances mesen teric and intestinal edema and probably inflammation of the hepatic parenchyma

Pain is a frequent early symptom in about half the patients with portal cirrhosis In two thirds of these it is located in the epigastrium over the liver or in the right hypochondrium usually appearing as a dull ache which is often intermittent and may be aggravated by exercise or food Radiation of pain to the shoulder is observed occasionally In patients with severe pain the liver is often tender Colicky pain is not un common and in view of the known tendency for gallstones to develop in cirrhotic patients presents a dificult diagnostic problem Enlargement of the spleen weakness weight loss and fatigability aid classification of the pain and facilitate diagnosis in the preascitic stage of cirrhosis Nonobstructive biliary or cholangiolitic cirrhosis is characterized by long standing regurgitation jaundice recurrent attacks of fever and upper abdominal pain Hepatomegaly and frequent occurrence of clubbed fingers aid differentiation of this type

Pain is often the initial symptom in primary carcinoma of the liver due partly to distention of the capsule

About 90% of pyogenic abscesses are accompanied by pain In the early stages it is usually dull constant and felt over the liver especially anteriorly or in the axillary line or in the epigastrium Sharp severe pain greatly aggravated by breathing is common in the later stages and is probably partly due to perihepatitis Points of radiation include the midback right loin and right shoulder area Localized intercostal pain with spot tenderness is common if the abscess lies close to

globulin 4 35 Gm Takata Ara 3 plus and cephalin flocculation test 2 plus Beginning three days after admission 2 Gm sulfadiazine was given daily for 12 days Temperature was normal the next day and remained so until discharge The patient was hospitalized the third time 16 months later after an episode of hematemesis Jaundice was pronounced and kin pale The liver appeared somewhat smaller and temperature was subfebrile During the fir t days in the hospital ascites developed Hemoglobin was 46% red cell count 2 400 000 albumin 3 4 Gm globulin 3 9 Gm van den Bergh direct 1 plus indirect 3 plus icteric index 50 cephalin flocculation test 1 plus Takata Ara 3 plus and thymol turbidity 10 On 200 000 units of



Fg 102—D pe po tal filt at nd pe i ctal fib os g w g f i m a H m i y) ×1 0 (C i y f R bm i w t M t oe t l gy 18 5 0 545 A g st 1951)

penicillin daily for 10 days the patient improved and ascites disappeared (Fig 101)

In all cases there was a distinct parallel between the intensity of jaundice and height of fever At no time was jaundice characterized by complete obstruction of bile flow possibly due to the patchy nature of the anatomic changes in the liver Liver biopsy in two cases indicated that periductal cell infiltration probably was important in producing jaundice (Fig 102) Small doses of sulfonamides produced remissions in all patients Fever disappeared within one or two days jaundice subsided liver function improved and general condition was favorably affected This effect lasted for weeks or

Jerusalem) reports five cases to illustrate the effect of small doses of sulfonamides on the clinical course Case 1 is given here

Man 18 hospitalized in 1945 gave a history of short attacks of dysentery at age 13 and 14 and discovery of an enlarged liver without other abnormal findings in 1941 He had attacks of right upper quadrant pain with high fever jaundice and itching 18 months before hospitalization Jaundice persisted the intensity varying with severity of pain Appetite was good there was no weight loss or lassitude On admission he was deeply jaundiced and had a fever of 103 1 F The liver filled the epigastrium extended a handbreadth below the costal margin and was firm but not tender

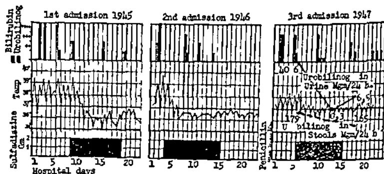


Fig 101 —Lit t t lf l d p ll n l l c (C t y f Rachmilewitz M G t t l gy 18 530 545 A g t 1951)

The pleen was also large and firm the lower border extending 4 cm below the costal margin Urine contained bilirubin and urobilinogen Stools contained no ova or parasites Hemoglobin was 70% red cell count 4 000 000 white cell count 7 000 with 70% neutrophils Sedimentation rate was 12 minutes Significant blood chemistry values included van den Bergh direct 3 plus indirect 2 plus icteric index 50 cholesterol 204 mg cholesterol ester 62 mg albumin 4 Gm globulin 3 9 Gm Takata Ara 1 plus and cephalin flocculation te t 1 plus

Findings suggested a diagnosis of biliary cirrhosis 10 days after admission a therapeutic trial was begun with 2 Gm sulfadiazine daily Temperature became normal the next day general condition improved and jaundice subsided icteric index dropped to 20 On discharge two weeks later the patient was advised to continue sulfadiazine He remained in good health for four months then relapsed Six months after relapse he was again hospitalized with epistaxis fever and jaundice Findings were essentially the same as on first admis ion Blood chemistry determinations revealed van den Bergh indirect 3 plus icteric index 75 albu[illegible]

ished salt output Edema fluid shifted to the abdomen with no change in body weight or electrolyte elimination after paracentesis in patients on 19 2 mEq sodium intake The fundamental ion is sodium not the chlorides since ammonium chloride administration does not significantly alter fluid retention

Salt restriction did not cause demonstrable salt depletion or oliguria however salt administration increased fluid retention body weight edema and ascites It is therefore concluded that salt restriction is indispensable to control and management of fluid retention in patients with ascites Repeated paracenteses and even more diuretics can be avoided by adequate restriction of the salt intake

Studies of Serum and Urine Constituents in Patients with Cirrhosis of Liver during Water Tolerance Tests Elaine P Ralli Stephen H Leslie George H Stueck Jr and Bertram Laken[3] (New York City) conducted 30 water tolerance tests on 7 normal subjects and 15 patients with cirrhosis of the liver *with and without ascites*

Procedure —The fasting patient was catheterized and then given 1,500 ml tap water orally Urine was collected at 30 minute intervals and tested for specific gravity and chloride concentration Fasting blood samples were collected and other samples were taken at periods coinciding with pronounced changes in rate of urine excretion Plasma volume total protein albumin and globulin serum chlorides serum sodium and serum water values were also determined for all subjects

Patients with cirrhosis showed a diminished capacity to excrete ingested water Whereas normal subjects excreted 100% in 180 minutes patients with cirrhosis without ascites did not show 100 % excretion during the entire 240 minute test period and at 180 minutes had excreted only 80% in patients with cirrhosis and ascites average water excretion at the end of the test was only 32% The minute volume of urine was decreased during the entire test in patients with ascites In those without ascites it decreased sharply when the peak of diuresis was reached The decreased capacity of patients with cirrhosis to excrete water was also observed after administration of 5% glucose

The most striking changes in serum constituents occurred in concentrations of sodium chloride During diuresis sodium

(3) Am J M d. 11 157 169 Aug t, 1951

months after stopping treatment before recrudescence of fever and clinical signs Experience indicates that a maintenance dose of 1 Gm sulfadiazine daily might control acute symptoms and keep the disease quiescent The chemotherapeutic effect achieved demonstrates the role of bacterial infection in the symptomatology and pathogenesis of chronic intrahepatic cholangitis even in the absence of definite bacteriologic etiology

Observations on Alterations in Electrolytes and Fluid Balance in Patients with Cirrhosis of Liver with and without Ascites were made by William E Ricketts Lillian Eichelberger and Joseph B Kirsner[2] (Univ of Chicago) Of seven patients studied 2 29 weeks four had ascites and edema and three were asymptomatic Cirrhosis was histologically confirmed in all by examination of needle biopsies Two normal individuals served as controls All studies were simultaneous made at regular intervals under conditions of constant daily intake of food calories water and electrolytes Sodium potassium and chloride concentrations in the serum and ascitic fluid were measured Additional analyses included serum CO_2 pH and nonprotein nitrogen total plasma protein albumin and globulin total protein plasma volume and hematocrit values of the ascitic fluid Total daily output of urine urinary sodium chloride and potassium was measured Studies were also made of the effects of reducing sodium intake to 19 2 and 37 3 mEq daily and of increasing it to 72 4 mEq of large water intake paracentesis and administration of diuretics and protein parenterally

As expected total plasma protein and albumin concentrations were decidedly depressed in all ascitic patients and normal in those with asymptomatic cirrhosis The same was true of urinary excretion of sodium chloride There was no relation between concentrations of electrolytes in serum or ascitic fluid and in urine In ascitic patients treated by long term protein repletion edema and ascites disappeared as did tendency to salt and water retention That the colloid osmotic pressure of the blood does not however regulate salt excretion by the kidney was suggested by the observation that albumin given intravenously although raising total circulating protein and albumin levels to normal did not correct dimin

(2) J Cl I t 30 1157 11 0 N mb 1951

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(3) Am. J Med. 11 157 169 August 1951

chloride concentration in the serum decreased when the minute volume of urine was decreasing there was an increase of 3% or more in serum sodium chloride in patients with cirrhosis compared with an average of 2 5% in controls Such an increase possibly stimulates secretion of the anti diuretic hormone thus accounting for the sharp decrease in minute volume of urine The authors suggest that the pre dominance of ascites in this disease is due to the combination of increased portal pressure increased capillary permeability and water retention associated with decreased urine output If the disease is not too far advanced spontaneous diuresis may be produced by a highly nutritious diet intensive vitamin therapy mercurial diuretics or a low sodium diet Once ascites requiring repeated paracenteses has occurred diuresis may be accomplished in some cases by persistent use of proper diet and intravenous administration of large amounts of special liver extract

[The two preceding articles are representative of a surprising number of current investigations of similar nature Most have been undertaken in an attempt to determine definitely the mechanisms involved in the formation of edema and ascites These researches will undoubtedly lead to a better understanding of the metabolic derangements with their im portant bearing on diagnosis prognosis and treatment —Ed]

Reversible Toxic Manifestations in Patients with Cirrhosis of Liver Given Cation Exchange Resins were noted by George J Gabuzda Gerald B Phillips and Charles S Davidson[4] (Harvard Med School) Clinical observations were made on 12 patients before during and after administration of am monium resin (4 patients) ammonium potassium resin (4 patients) and hydrogen resin (4 patients) given as treatment for ascites and edema During 18 courses of 30 90 Gm daily in divided doses for 3 13 days 10 patients had significant diuresis with reduction of ascites edema and body weight

Neurologic disturbances were noted eight times in six of the eight patients on ammonium containing resins Disturb ances even three days after start of therapy consisted of drowsiness apathy weakness slurred speech disorientation confusion inappropriate behavior and a coarse irregular flapping tremor intensified by sustenance of posture In two patients the changes were noted during the first course of resin cleared promptly when resin was discontinued and

(4) New England J Med 246 124 130 Jan 24 1952

recurred when therapy was resumed Tremor ordinarily ap peared first and outlasted changes in mental status ch inges quickly reversed when resin was stopped Neurologic compli cations did not correlate with change in serum sodium or potassium concentrations or with degree of acidosis hence they could not definitely be attributed to these alterations In contrast two patients given hydrogen resin had typical clinical manifestations of hypokalemia and acidosis without the neurologic abnormalities of patients given ammonium containing resins

Constipation and fecal impaction are a frequent compli cation of resin therapy and must be seriously considered in patients predisposed to massive bleeding from esopha eal varices or hemorrhoids Other complaints included epigastric burning in one instance anorexia in another and leg cramps in two

The study indicated that the cation exchange resins in vestigated are poorly tolerated by patients with severe liver disease and should be prescribed with caution if at all The e resins do not replace adequate diet with rigidly restricted sodium content as the best method of managing ascites and edema in patients with liver disease Similarity of tremor and mental changes observed in patients given ammonium con taining resins to neurologic manifestations of threatened hepatic coma suggests a common biochemical basis

Value of Liver Function Tests in Diagnosis of Intrahepatic Metastases in Nonicteric Cancer Patient Mortimer L Mendel sohn and Oscar Bodansky[5] (Memorial Hosp New York City) reviewed the records of 160 nonicteric adult cancer patients 99 with proved liver metastases and 61 without metastases who served as controls Liver function tests were performed some weeks after metastatic involvement of the liver had been established rather than immediately after surgery The meta static cases were then broken down into subgroups according to estimated extent of involvement at operation or autopsy one or several nodules in the liver constituted tage I numer ous nodules stage II and extensive involvement with little normal liver tissue intact stage III

It was found that the serum protein blood urea nitrogen thymol turbidity total cholesterol hemoglobin values and

(5) C nc 5 1 8 J a y 1952

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[The two preceding articles are representative of a surprising number of current investigations of similar nature Most have been undertaken in an attempt to determine definitely the mechanisms involved in the formation of edema and ascites These researches will undoubtedly lead to a better understanding of the metabolic derangements with their im portant bearing on diagnosis prognosis and treatment.—Ed]

Reversible Toxic Manifestations in Patients with Cirrhosis of Liver Given Cation Exchange Resins were noted by George J Gabuzda Gerald B Phillips and Charles S Davidson[4] (Harvard Med School) Clinical observations were made on 12 patients before during and after administration of am monium resin (4 patients) ammonium potassium resin (4 patients) and hydrogen resin (4 patients) given as treatment for ascites and edema During 18 courses of 30 90 Gm daily in divided doses for 3 13 days 10 patients had significant diuresis with reduction of ascites edema and body weight

Neurologic disturbances were noted eight times in six of the eight patients on ammonium containing resins Disturb ances even three days after start of therapy consisted of drowsiness apathy weakness slurred speech disorientation confusion inappropriate behavior and a coarse irregular flapping tremor intensified by sustenance of posture In two patients the changes were noted during the first course of resin cleared promptly when resin was discontinued and

(4) New England J Med. 246 124 130 Jan 24 1952

was 80% higher than the normal of 143 μg 12 patients had levels above normal and 4 had levels of 360 480 μg In the three women menstrual history was abnormal so that much less blood was lost during the reproductive period There was no evidence that toxic factors played a role in producing hemochromatosis

In 18 patients the skin was of fine texture and shiny or thin and dry in all but 1 the typical bluish gray pigmentation was present Weakness easy fatigability and lack of energy were present in all There was an abrupt decline in the libido in 9 of the 13 men In 10 of 17 patients there was virtually no body hair except for the pubic hair and in half the patients the latter was of typical feminine distribution Three patients had moderate reduction of hair and four had normal hair All the men had to shave less often All patients said that the hair features had been present for as long as they could remember There was a history of indigestion in 12 patients in 2 it was due to a peptic ulcer

The liver was palpable in all but 1 patient in 13 it was enlarged 8 cm or more below the costal margin the spleen was palpable in 6 patients Complications of hepatic cirrhosis were present five each had ascites and spider nevi three each enlarged superficial abdominal veins and hematemesis (one of the latter on autopsy had esophageal varices) and four subcutaneous ecchymoses There is moderate impairment of hepatic function by the time cirrhotic changes can be demonstrated histologically There was slightly raised serum bilirubin level in seven moderately elevated serum alkaline phosphata e in seven and prolonged prothrombin time in three Total serum albumin of seven was less than 4 Gm Thymol turbidity was high in four and slightly abnormal in eight The thymol flocculation was negative in all The gamma globulin was increased in 8 of 15 patients The reactions to intravenous hippuric acid showed liver impairment in two thirds of the patients Surprisingly the cephalin flocculation was abnormal for only three patients two of whom had died before the study Negative findings on liver function tests do not rule out the presence of hemochromatosis in the pre cirrhotic stage

Diabetes was present in 18 9 of whom took insulin None showed undue tendency to acidosis and in only one was there

white cell count were not significantly affected by metastases Cephalin flocculation and bilirubin values were significantly more abnormal in metastatic patients 31% and 28% exceeded normal values as compared to 15% and 12% in controls However because ranges were so similar these tests could not be used as criteria for differential diagnosis although functions represented by these tests are affected by liver metastases By contrast the serum alkaline phosphatase and bromsulfalein retention tests yielded results sufficiently different to classify individual cases Of 50 patients with metastases and normal serum bilirubin values 39 (78%) had elevated phosphatase values Moreover incidence of abnormality and average values increased progressively from stage I to stage III Phosphatase activity was elevated in 21 (91%) of 23 patients with moderate to severe hepatomegaly Since all 29 control patients had phosphatase concentrations below 5 4 units and 34 of 50 metastatic patients exceeded this level presence or absence of liver metastases was correctly diagnosed on the basis of phosphatase value in 63 (80%) of 79 cancer patients Similar manipulation of only metastatic patients without hepatomegaly resulted in 73% correct diagnoses with 44% phosphatase values above the highest control figure In the bromsulfalein test 20% of metastatic values exceeded the highest control value However results were all from patients with advanced metastatic disease as estimated by liver size or operative findings In the patient without hepatomegaly the bromsulfalein test did not differentiate between metastatic and nonmeta tatic disease

The serum alkaline phosphatase test is the most di ect and only helpful standard liver function test for evaluation of extension of cancer to the liver However it is invalid in patients with bone metastases (or other proliferative bone disease) or in patients with jaundice or primary liver disea e

Hemochromatosis T L Althausen (Univ of California) R K Doig S Weiden R Motteram C N Turner and A Moore[6] (Melbourne Australia) studied 20 men and 3 women with hemochromatosis 15 were studied intensively 4 could not be seen personally and 4 had died Intake of alcohol was excessive in 10 of 20 patients who gave information about drinking Average level of iron in the serum of 18 patients

(6) A M A A h I t M d 88 5 3 5 0 Nov mb 19 1

dia tase values revealed that a constant mathematical re lationship did not exist although the curves were parallel in general contours The maximal urine diastase level for each attack and time of return to normal were usually re corded simultaneously with corresponding blood values In five patients the sequence of blood and urine diastase levels suggested transient impairment of renal function After this was noted subsequent blood and urine samples were also analyzed for creatinine content Four of the patients had a sharp fall in both blood and urine diastase values followed by a retarded fall of blood diastase increase in rate of urine diastase excretion and progressive return of both blood and urine diastase values to normal While the blood diastase level was falling at a diminished rate the creatinine excretion was also lower

The authors concluded that the time elapsed before elevated blood diastase results in increased urinary excretion of diastase in the presence of normal renal function is less than two hours and is probably a matter of minutes Impair ment of renal function which commonly occurs during an attack of transient acute pancreatitis even in absence of clinical shock is usually greatest from 24 to 48 hours after onset and lasts 12 36 hours

Acute Pancreatitis and Its Treatment An avoidably high *mortality rate results from clinical failure to recognize acute* pancreatitis and to treat it correctly Mims Gage and George Gillespie[8] (Tulane Univ) believe that unless associated with certain viral diseases it is a chemically produced acute in flammatory condition caused most often by regurgitation of bile from the common duct gallbladder or both into the pancreatic ducts under enough pressure to rupture the inter lobular ducts and acini Symptoms are sudden in onset pro gressive and unremitting except when pent up toxic fluid has been drained off from the extrahepatic biliary system and pancreas In the latter sudden relief results from opening the papilla of Vater by dislodging the obstructing stone and/or relaxation of the sphincter of Oddi The first symptom—sudden unbearable pain in the epigastrium—is followed by nausea vomiting increased pulse rate shock of varying severity mild to moderate abdominal rigidity abdominal

(8) S th. M J 44 769 7 5 Sept mbe 1951

any difficulty in stabilization with diet and insulin Pancreatic function tests in many patients showed impairment in digestion of gelatin and hypersecretion of a dilute pancreatic juice in response to stimulation with secretin The significance of these findings is uncertain

Biopsies of the liver in 21 patients showed that examination of the liver provides a definite criterion for establishing a diagnosis of hemochromatosis In most cases there was a multinodular cirrhosis with hemosiderin present in gross amounts in the parenchymal cells Hemosiderin was present in all 11 patients in whom gastric biopsies were done In nine patients the gastric mucosa except for the hemosiderin was normal in two there was some atrophy of the cells Biopsy of the skin in 13 patients showed no hemosiderin in the epidermis but the melanin content of the cells in the basal layers was increased this accounted for the bluish gray appearance of the skin

Hemosiderosis is rare in females probably because the normal loss of iron in menstrual blood prevents its appearance Changes in libido and the male sex organs as well as the sparsity of body hair in males with hemochromatosis and with ordinary portal cirrhosis may be due to excess estrogen through failure of the liver to destroy the estrogen This explanation is not likely in hemochromatosis because of the relatively good liver function The sexual regression may be due to long standing malnutrition Diabetes associated with hemochromatosis usually does not present difficulty in stabilization with diet and insulin

Early diagnosis of hemochromatosis depends on the physician s alertness for skin pigmentation sparsity of body hair unexplained hepatomegaly and weakness A suspicion of hemochromatosis is best confirmed by biopsy of the liver or of the gastric mucosa

Interrelationship of Blood and Urine Diastase during Transient Acute Pancreatitis Arnold Dankner and Carl J Heifetz[7] (Jewish Hosp St Louis) observed 12 patients during 13 attacks of acute pancreatitis A blood sample and an accurately timed 1 2 hour urine sample were obtained as soon as the disease was suspected and at 12 hour intervals thereafter Comparison of corresponding blood and urine

(7) G t oent ol gy 18 07 217 J 1951

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(8) South M J 44 769 775 Sept mbe 1951

tenderness cyanosis of the face and bluish patches on the abdomen and extreme prostration Initially normal or subnormal temperature may rise to 100 102 F on the second or third day If temperature becomes normal and then begins to rise in about a week becoming picket fence in type bacterial suppuration or development of abscesses in devitalized pancreatic tissue should be suspected Significant diagnostic points present in all cases are the excruciating epigastric pain and elevated blood amylase content and sedimentation rate A roentgenogram of the abdomen has been reported to show a sentinel loop of dilated small intestine usually in the upper jejunum located in the upper central or upper left quadrant of the abdomen

Surgery in the acute phase is now considered inadvisable Instead hydration should be attained by giving 2 500 3 000 cc glucose and saline intravenously in 24 hours Calcium gluconate should be added to the infusion after taking blood samples for chemical examination including amylase electrolytes and carbon dioxide determinations Blood transfusions should be given and a duodenal tube inserted for drainage of the upper gastrointestinal tract Nothing should be given orally until adequate pyloric balance is established Antibiotics must be used freely Release of the pent up necrotizing fluid by relieving obstruction of the ampulla of Vater may be achieved by bilateral splanchnic block with 20 30 cc of 1% procaine hydrochloride Patients in shock should have only right splanchnic block since bilateral block will cause a drop in blood pressure Within 20 minutes of bilateral splanchnic block the patient is dramatically relieved of pain in some cases two or more blocks may be necessary Surgical treatment of concomitant gallbladder and extrahepatic duct disease should be deferred until the patient has completely recovered from the acute phase

Consideration of Lethal Factors in Acute Pancreatitis is presented by Vinton E Siler and John H Wulsin[9] This disease falls into three general clinicopathologic subtypes (1) Acute interstitial pancreatitis ordinarily self limiting and rarely fatal identified at operation or autopsy by induration and swelling of the pancreas without softening or hemorrhage Without anatomic verification the acute pancreatitis patient

(9) A M A Arch S g 63 496 504 O t be 1951

arbitrarily falls in this classification if the clinical course is benign and if there is no evidence of hemorrhage necrosis or suppuration in and around the pancreas (2) Acute pancreatitis with hemorrhage and necrosis (3) Acute pancreatitis with suppuration or pseudocyst characterized by intra abdominal mass Distribution and mortality rate in each group as seen in 164 patients with acute pancreatitis admitted to Cincinnati General Hospital 1941 50 are shown in the table

The authors analyzed 22 fatal cases in each of which operation or autopsy was performed (autopsy in 91%) Two

CLINICOPATHOLOGIC CLASSIFICATION AND MORTALITY RATE

Clinicopathologic Type	No Cases	No Deaths	Mortality %
Hemorrhagic	15	12	80 0
Suppurative (pseudocyst)	18	6	33 3
Interstitial	130	4	3 1
Unclassified	1	1	100 0
Total	164	23	14 0

thirds were in patients 51 or older 14 (63%) were women No difference in racial incidence was noted between fatal and nonfatal cases Abdominal pain was the chief initial complaint This was generally prominent in the upper abdomen but in some patients it was generalized and in others in the lower part if retroperitoneal inflammation had already spread extensively Peripheral circulatory collapse (evidenced by clammy pale or cyanotic skin weak rapid pulse and low or no apparent blood pressure) was noted in 10 patients although 7 responded temporarily to transfusions and fluids given intravenously peripheral circulatory collapse was irreversible in 30 Only one third of patients who died had temperatures of 100 F or more when first seen but terminal pyrexia was a common and ominous sign Four patients showed jaundice at hospitalization or later and in all but three the abdomen was generally tender with maximal sensitivity in the upper quadrant corresponding to site of severest pancreatic damage Routine laboratory tests were nonspecific

In 14 patients correct diagnosis was not established until at surgery or autopsy because either the serum amylase test had not been used or had been improperly interpreted Slight to moderate increase in serum amylase values was found in 10 fatalities before operation or autopsy and remained elevated

instead of falling within a day or so as it did when the course was benign Contrary to expectation greatly increased values found in a number of patients with the interstitial form of disease were not indicative of fatal prognosis

The clinical course of the disease varied in length 11 (50%) died within two days of hospitalization 6 others within 10 days and 5 after several weeks Ominous prognostic signs were peripheral circulatory collapse and gastrointestinal hemorrhage at or during hospitalization Circulatory collapse accompanied 13 deaths a gradual downhill course marked by fever and terminated by sepsis and asthenia resulted in 9 more Death could not be attributed to any one causative factor common to all cases Remediable causes of death are presently found in suppurative pancreatitis Fatal abscess formation with gastrointestinal hemorrhage might be prevented by taking proper surgical measures In general fatalities can be prevented by surgical drainage of pancreatic abscesses and measures to avoid development of the hemorrhagic and necrotic forms of the disease Necrotic disease often results from improper treatment and unnecessary surgery for the mild interstitial type Frequent and repeated serum amylase analyses would aid the clinician in administering correct therapy Careful supervision of the patient after pancreatitis attack and interval cholecystectomy when the gallbladder is diseased will also help lower death incidence

[The three preceding articles on acute pancreatitis are indicative of the widespread current interest in this disease Suspicion of the disease by an alert profession coupled with a reliable laboratory diagnostic aid (serum amylase test) disclose many instances of the acute form which formerly went unrecognized Great progress has been made in treatment because of increased knowledge of the local pathologic process even though etiology is not yet clarified —Ed]

Studies in Pancreatic Function IV Use of Secretin Test in Diagnosis of Tumors in and about Pancreas The biochemical approach to diagnosis of pancreatic tumors depends on disturbances in pancreatic endo and exocrine function In a preliminary study using the secretin test Dreiling and Hollander concluded that pancreatic tumors produce an alteration of pancreatic secretion which depends on the site and degree of pancreatic duct obstruction caused by the tumor David A Dreiling and Alice Klein[1] (Mt Sinai Hosp) present

(1) Gast oent r l gy 18 184 196 J 1951

an additional study of secretin test results on 61 patients with pancreatic tumor

PROCEDURE —A double lumened gastroduodenal tube is introduced into the duodenum of the fasting patient under fluoroscopic control After a control collection period of 20 minutes one clinical unit of secretin/kg body weight is given intravenously Gastric and duodenal aspirates are then obtained fractionally by continuous suction for 80 minutes and the following determinations are made total volume maximal bicarbonate concentration amylase concentration and total amylase secretion guaiac reaction and biliary pigment concentration The first three characterize pancreatic response to secretin

The most consistent and pronounced abnormality was depression of the volume response observed in 53 patients Bicarbonate values were usually slightly depressed Total amylase secretion was least affected and such decrease as was found was primarily a result of low volume due to obstruction of pancreatic flow Thus alteration of pancreatic secretion tended to be quantitative rather than qualitative the reverse of what is characteristic for diffuse inflammatory pancreatic disease The greatest decrease in secretion occurred in patients with diffuse pancreatic lesions These lesions in addition to producing pancreatic duct obstruction also destroy the secreting parenchyma Secretin response associated with these tumors cannot always be differentiated from that occurring with chronic pancreatitis Alteration of secretion in patients with localized tumors was less pronounced being some greater when the tumor was in the head than in the body of the pancreas When the lesions were in the tail results were essentially normal they were also normal when malignant lesions were present in organs contiguous to but not invading the pancreas

The biliary pigment and pancreatic response to secretin proved valuable in localizing pathologic involvement in patients with obstructive jaundice and pancreatic tumors If jaundice is absent and pancreatic volume decreased (normal biliary pigment and abnormal pancreatic response) the lesion is in the head or body of the pancreas If jaundice is present with decreased pancreatic volume (abnormal biliary pigment and pancreatic responses) the lesion is in the head of the pancreas and obstructs both pancreatic and biliary tracts With obstructive jaundice and a normal pancreatic volume

(abnormal biliary pigment and normal pancreatic response) the lesion involves the extrahepatic ducts however these findings may also occur with nonmalignant common duct obstruction when an obstructing stone lodges in the narrowed terminal part of the common duct above the duct of Wirsung Diabetes mellitus was present in 22 of the 61 patients Since diabetes per se produces no alteration in pancreatic secretion an abnormal secretin response in a diabetic is presumptive evidence of pancreatic tumor or pancreatitis

Relationship between Relapsing Pancreatitis and Essential Hyperlipemia was investigated by Gerald Klatskin (Yale Univ) and Martin Gordon[2] (V A Hosp Newington Conn) Hyperlipemia occasionally occurs with attacks of pancreatitis usually of the chronic relapsing variety Xanthomatosis of the skin of the eruptive type and lipemia retinalis are recog nized manifestations of hyperlipemia The former has been observed before onset of abdominal pain in some cases sug gesting that the hyperlipemia may precede the pancreatitis In this group the early age at which the pancreatitis appears is distinctive in striking contrast to the age incidence found in more common types of relapsing pancreatitis which gen erally affect the middle aged and seldom occur in early life

A case of relapsing pancreatitis with hyperlipemia and xanthomatosis was studied in a man 22 who had sudden severe pain localized to the upper left quadrant four years after a laparotomy for acute necrotizing pancreatitis Evidence indicated that the hyperlipemia was familial in nature that it antedated the onset of abdominal pain and that its severity which could be controlled by dietary regulation was an im portant factor in precipitating the relapses of pancreatitis

It was concluded that when relapsing pancreatitis and hyperlipemia occur together pancreatitis is the result rather than the cause of the hyperlipemia and that both are mani festations of the hereditary disorder known as essential hyper lipemia Experiments designed to elucidate the mechanisms underlying the pathogenesis of pancreatitis in such cases were inconclusive However there is evidence that the relapsing pancreatitis and other abdominal crises which occur in es sential hyperlipemia may be the result of alterations in the

(2) Am. J Med 12 3 23 J u y 195

physical state of serum lipids leading to vascular occlusions by clumped lipid particles

THE INTESTINAL TRACT

Observations on Effect of Drugs on Intestinal Intubation are presented by Meyer O Cantor and Harold P McGinnes[3] (Grace Hosp Detroit) Each instance of unsuccessful intubation was analyzed as to the probable cause for failure and the drug was then selected which would most likely produce success Morphine and atropine proved effective in intubating the nervous high strung apprehensive patient who becomes panicky at the mere sight of a long intestinal tube On 10 specific occasions when routine intubation failed in this type patient administration of 10 mg morphine sulfate and 0 45 mg atropine sulfate resulted in success The effectiveness of these drugs is attributed to the mild euphoria and feeling of well being which morphine produces and to the antispasmodic action of atropine Prostigmin® and urecholine® were found to be effective in patients presenting atony of the small bowel or paralytic ileus Both drugs by virtue of their effect on the small bowel were found to speed up the downward progress of an intestinal tube that had already passed through the pylorus Urecholine® was especially useful in elderly patients with gastric as well as intestinal atony and was used even with the tube in the stomach because of its effect on gastric motility Intubation was successful immediately in all patients so treated

Use of octin® in patients in whom the tube head would not pass through the pylorus despite correct positioning was suggested by the report of Filho who noted that the drug relaxed the pyloric sphincter permitting 90% successful intubations in 30 minutes or less Because such patients are uncommon it was decided to use octin® during intubation of the first 10 patients admitted to the hospital In five intubation was unsuccessful within 24 hours after injection of 0 1 Gm octin® hydrochloride Three had complete obstruction and had not been operated on before intubation two had been operated on one to two days previously Five patients successfully passed the long tube

(3) G s oe t 1 gy 29 516-525 N mbe 1951

through the pylorus in one to two hours after receiving the drug Of these two were intubated for postoperative ileus in both the routine method had failed These patients presented evidence of pylorospasm (Fig 103) An additional patient had



Fg 103—O h ft f xct ® hy f ochl de p t t h m t nt l t w un f l f tw d y (C t y f C to M O d McG s H P G t t l gy 19 516 525 \ mb 1951)

a localized small bowel obstruction with an acute abdominal condition In the other two patients a long tube was passed as a preoperative measure before elective bowel surgery The authors believe that octin® should be reserved for patients in whom failure of intubation is due to pylorospasm

Intestinal Bleeding Associated with Acetylsalicylic Acid. Walter Modell and Russell Patterson[4] (Cornell Univ) report a case

Man 74 had continuous intestinal bleeding of undetermined origin for eight years associated with anemia and weakness During this period a polyp hiatus hernia and carcinoma of the colon were discovered each when found was thought to be the cause of bleeding The patient had been in the habit of taking about 3 Gm. acetylsalicylic acid daily for many years to relieve pain caused by osteoarthritis of the right knee. Without iron therapy hemoglobin levels ranged from 7 to 9 Gm. and red blood cell counts from 3,500 000 to 5 000 000 When the patient was given ferrous sulfate orally 1 1 5 Gm. three times daily and a diet rich in vitamins and meats the hemoglobin level rose despite continued bleeding To test the effect of acetylsalicylic acid the patient was followed for almost one year on alternating periods with and without salicylate Each time about two to three days after he discontinued the drug gross blood disappeared from the stools. About two weeks after its administration was resumed, blood was seen in the stools. The dose of iron remained constant throughout. The patient voluntarily discontinued taking acetylsalicylic acid because of its effect. He has since had no blood in the stool and the hemoglobin level is normal without iron therapy

Although a platelet count of 120 000 was found after two weeks of acetylsalicylic acid therapy another count of 215 000 was obtained after a similar period The possibility that intestinal bleeding was associated with thrombopenia rests therefore on the single low platelet count though the etiologic connection with salicylates seems definite

Detection of Occult Blood in Feces Including Observations on Ingestion of Iron and Whole Blood. Because cancer detection clinics need a simple rapid screening method to exclude malignancy of the gastrointestinal tract Ann Peranio and Maurice Bruger[5] (New York Univ Post Grad Med. School) compared sensitivity of four occult blood indicators (orthotolidin benzidine phenolphthalein and guaiac) and investigated the effect of ingestion of iron and whole blood in both stool and urine

Method.—A homogeneous specimen of feces about the size of a large pea was added to 4 ml. water After the mixture was heated and cooled 1 ml was used for each test. Measurements were exact and constant to insure comparable results The orthotolidin test (hematest® tablet method) was performed as outlined by the manufacturer and the result read in two minutes In the benzidine test

(4) J A. M A. 147 1 4-1 6 Sept 8 19 1
(5) J Lab. & Clin. Med. 38 433-445 September 19 1

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(4) J A. M A 147 124 126 Sept 8 1951
(5) J Lab & C n M d 38 433 445 Sep mber 1951

1 ml stool emulsion was mixed with 1 5 ml glacial acetic acid containing a pinch of benzidine and 5 drops of 3% hydrogen peroxide was added dropwise with shaking The reaction took two minutes For the guaiac test 1 ml emulsion was added to 2 ml glacial acetic acid then 2 ml ether and 2 ml alcoholic guaiac solution (1 Gm in 60 ml 85% ethyl alcohol) were added Five drops of 3% hydrogen peroxide was added dropwise with shaking and the result read immediately The phenolphthalein test of Meyer was performed as described by Gettler and Kaye

The orthotolidin benzidine and phenolphthalein tests require meat and fish free diet for 72 hours, the guaiac test does not

Ingestion of ferrous sulfate causes no false positive reactions except possibly with orthotolidin but other substances unrelated to blood may produce color interference or false positive reactions Mild gum bleeding will not produce positive reactions The following amounts of ingested whole blood will produce positive reactions orthotolidin 1 ml benzidine and phenolphthalein 3 5 ml and guaiac 20 ml Normal subjects on unrestricted diets will show faintly positive reactions to guaiac after ingestion of 2 3 ml blood

The orthotolidin test is most sensitive but because of frequent false positive reactions is misleading The benzidine test second in sensitivity frequently gives false positive reactions unless the quantity of benzidine is restricted Phenolphthalein is third in sensitivity and guaiac last

Morphologic Consequences of Acute Exogenous (Staphylococcic) Gastroenteritis on Gastric Mucosa Eddy D Palmer[6] (Walter Reed Gen l Hosp) examined 42 patients at various intervals during and after acute staphylococcic food poisoning Gastroscopy was done in all and biopsy of the mucosa in 24 In six patients biopsy and gastroscopy were done in the early stage of illness The rest were examined at intervals after vomiting had ceased Duration of illness was measured from onset of initial symptom

Acute exogenous gastritis was observed in 13 patients In the acute stage hyperemia edema muscular irritability erosion petechiae and purulent exudate were found in seven and varying symptom combinations in the rest The hard fiery hyperemia was patchy in distribution with intervening areas of pale succulent edema Muscular irritability was re

(6) Gastroenterology 19 462 475 November 1951

flected by frequent segmental spasms across the pars media and in all patients by absence of rhythmic peristalsis in the antrum Erosions and petechiae were common ordinarily seen as small groups in the pars media They were rarely seen in the antrum and never in the fundus The abundant purulent exudate was thin and gray running between the rugae and consisted of leukocytes surface mucous cells sheets of mucous epithelium and erythrocytes

Five hours after onset biopsy in one patient revealed normal gastric mucosa In another the mucosa was intact eight hours after onset but the foveolar layer was packed with extruded glandular cells Changes found in other patients on the first day of illness consisted of desquamation of glandular cells into the foveolae an occasional focus of sub acute inflammation in the neck region and early necrobiosis at the junction of gland and foveolae Masses of glandular cells were extruded to the surface from the foveolar lumen Separation of the foveolar layer was associated with subse rosal edema and hyperemia On the second day exfoliation was more advanced and resulted in disruption of surface integrity Superficial erosions acute and chronic inflammatory infiltra tion and edema were present Biopsy specimens from three patients on the third day were normal but three others showed some degree of necrobiosis and inflammation Depths of glands and regional interstitial tissue were never changed and the muscularis mucosa was normal in all specimens

After 80 hours gastroscopy showed normal stomachs ex cept for antral irritability or isolated patches of edema It was concluded that the sudden severe damage which is secondary to acute staphylococcic food poisoning produces no permanent morphologic abnormality in the gastric mucosa

Bacitracin Therapy in Chronic Bacillary Dysentery The problems of chronic bacillary dysentery are much more diffi cult than those of the acute type with its superficial pathologic picture The organisms are encysted in the bowel wall form ing pustules pits and scars Daniel N Silverman[7] (Southern Baptist Hosp New Orleans) presents data on 14 patients taken from a much larger series who were treated with bacitracin The antibiotic was given orally in doses of 40 000 units three times a day for 8 days to some patients and for 30

(7) G t oe i J gy 19 3 0 325 Octobe 1951

days to others The longer period of treatment was used early before adequate dosage was established Therapy showed the same effectiveness against varying strains of Bacillus dysenteriae including Shiga Flexner and Duval Sonne

Results were uniformly good with negative cultures and no symptomatic relapse for three months to three years after treatment Inflammation ulceration and lymphadenopathy which had been present before treatment disappeared No toxic symptoms were observed

[The opinion of the author and others notably Felsen that acute bacillary dysentery may give rise to sequelae of a chronic nature apparently is in disagreement with the viewpoint of those who maintain that such complications are rare In the discussion Felsen advocated use of the divided culture plate method in testing for antibiotic sensitivity Sensitivity was greatest with chloramphenicol and terramycin Treatment with chloramphenicol may be contraindicated in view of the increasing number of reported cases of aplastic anemia following its use —Ed]

Gastrointestinal Allergy Simulating Regional Enteritis Report of a Case is presented by George I Blumstein (Temple Univ) and Julian Johnson[8] (Univ of Pennsylvania)

Man 26 was hospitalized because of midabdominal cramping pain for eight hours with nausea but no vomiting He had had one loose stool There were right lower quadrant tenderness and mild rigidity The white blood cell count was 13 400 with 70% neutrophils and 2% eosinophils He had had three previous attacks and the family physician had considered the possibility of gastrointestinal allergy Mild asthma had been present since age 5 precipitated by respiratory infections but there were no known allergies The father s family was markedly allergic Right lower quadrant findings persisted the next day and rebound tenderness was noted The white cell count rose to 16 000 with 67% neutrophils and 7% eosinophils Because of the possibility of acute appendicitis operation was performed The appendix was normal but 500 cc clear fluid was found The terminal ileum was greatly thickened and edematous suggesting subacute terminal ileitis About 45 cm was resected with the right colon and an ileotransverse colostomy was performed

Microscopic sections showed pronounced edema of the submucosa and subserosa The entire wall was infiltrated by myriads of eosinophils but there was no evidence of ulceration or ordinary pyogenic infection The mesenteric lymph nodes also showed dilatation of sinusoids with edema and eosinophilic infiltration

The patient made an uneventful recovery but had three more attacks in four months all after ingestion of seafood He avoided seafood thereafter and had no further attacks

Diagnosis of gastrointestinal allergy is not considered valid unless the cause effect relation between the allergen and the

(8) J A M A 147 1441 1443 Dec 8 1951

symptoms is established Peripheral eosinophilia or x ray demonstration of gastric retention abnormal intestinal motility with small bowel segmentation and decreased luminal caliber should suggest the condition This case fulfilled the necessary requirements It demonstrates the possibility of confusing regional enteritis and gastrointestinal allergy on gross exam ination rather than indicates any etiologic relation between them

Clinical Significance of Nondysenteric Intestinal Amebiasis M J Miller (McGill Univ) and A Gilani[9] (Calcutta) pre sent evidence suggesting that nondysenteric intestinal ame

EFFECT OF ANTIAMEBIC THERAPY IN PATIENTS PASSING CYSTS OF E HISTOLYTICA

C x N	R y E H L I A	A M C T M N	R S T MENT
1	Small	Carbarsone	No improv
2		Carbar one enteroquinol	
3		Emetine sulfasuxidine® penicillin	Improved
4		Carbarsone enterovioform	No improv
5	Large	Penicillin sulfaguanidine enterovioform	
6		Diodoquin® emetine sulfasuxidine® penicillin	Improved
7	Small	Enteroquinol	No improv
8	Large	Pen cillin sulfaguanidine emetine en teroquinol	Improved
9		Enterovioform	?

biasis infections are asymptomatic Previous work by Sapero and Miller indicated that such symptoms as abdominal pain and tenderness and disturbance of bowel movements tended to occur more often in patients with Endamoeba histolytica infections than in noninfected persons

Of 36 patients hospitalized for gastrointestinal symptoms without evidence of organic disease 9 were proved to have E histolytica infection and were given amebicidal drugs as well as symptomatic treatment Infection free patients were all treated symptomatically Eight of the nine infected pa tients were followed during and for periods ranging from two weeks to two months after treatment Post treatment stools remained uninfected throughout observation Three patients improved with relief of symptoms but the other five responded little or not at all to therapy (table) Of the uninfected group 14 improved but 13 had little or no relief of symptoms

(9) T R y Soc T p M d & Hyg 45 131 136 Augu t 1951

Clinical picture differed little between the groups The common complaints—disturbance of bowel movements flatulence abdominal pain and loss of weight and strength—were about equally distributed among infected and noninfected patients Sigmoidoscopy of infected patients revealed several small erosions in the distal sigmoid in one and patchy mucosal congestion of the rectum and sigmoid in one No amebas were found in material removed from the suspect area in either case

A comparative study was made of the charts of 90 infected patients and 90 noninfected patients All histories stressed chronic gastrointestinal complaints but indicated no organic disease Disturbed bowel movements abdominal pain tenderness and discomfort flatulence acidity and mucus in the stool were the chief complaints in both groups indeed a higher incidence of these symptoms was found in the uninfected group

Although the study suggests that E histolytica did not influence symptomatology of nondysenteric intestinal amebiasis further work is necessary with larger groups and more carefully controlled treatment

Amebiasis Evaluation of New Therapies After finding that quinacrine was useful in the management of amebiasis Ryle A Radke[1] studied the effect of carbarsone combined with this drug from the standpoint of eliminating the cystic stage The effects of chloroquine and aureomycin were also studied

Endameba histolytica was found in rectosigmoid lesions or in the feces of all patients studied All had sigmoidoscopy immediately after treatment and again in 30 90 days At least three negative smears and a culture were taken before the bowel was presumed normal Failure of lesions to heal during treatment indicated treatment failure despite negative smears and cultures Dosages used were quinacrine 0 1 Gm four times daily for 15 days carbarsone 0 25 Gm three times daily for 10 days chloroquine 0 25 Gm four times daily for 15 days aureomycin alone 0 5 Gm four times daily for 7 days aureomycin with quinacrine and carbarsone 0 25 Gm twice daily for 5 days For women and children the dosage was proportionately less Patients were divided for treatment

(1) U S Armed F ces M J 2 1231 1 34 A g t 1951

as in the table with 35 in group 1 38 in group 2 35 in group 3 and 33 in group 4 Five in group 1 three in group 2 one in group 3 and all in group 4 had been treated unsuccessfully by other means

Patients in group 1 were usually symptom free in five days Complications were yellow skin and occasional nausea and emesis which were relieved with bed rest and cessation of therapy and did not recur when treatment was resumed The failure rate was 11% (table) In group 2 bowel symptoms improved in five to seven days In almost every patient however inability to focus the eyes longer than a few seconds

COMPARATIVE TREATMENT FAILURE RATES

Group	Treatment	Failure %
1	Quinacrine and carbarsone	11
2	Chloroquine and carbarsone	78
3	Aureomycin	65
4	Aureomycin quinacrine and carbarsone	12

developed Also most patients had severe nausea and vomiting which lasted till treatment was stopped When bowel symptoms improved in group 3 they did so within two days Nausea vomiting and diarrhea occurred in half the patients Patients in group 4 usually improved in two days Side effects were similar to those in the other groups They disappeared when treatment was stopped and did not return when it was resumed

Comparative results suggest that a combination of quinacrine and carbarsone with aureomycin in severe and resistant cases is effective in amebiasis A patient with amebic hepatic abscess was treated with quinacrine and carbarsone and two others one with pleuropulmonary involvement were similarly treated with the addition of aureomycin All recovered without surgical intervention except for paracentesis on the patient with pleuropulmonary involvement

[The choice of drug is largely made in the light of the physician s individual judgment experience and prejudice Prophylaxis also deserves consideration because amebiasis is a well recognized epidemiologic problem in many institutions Both the therapeutic and the prophylactic efficacy of milibis® and aralen® combined in tablet form were extolled by Berberian *et al* (J A M A 148 700 1952) —Ed]

Stasis of Appendix as Cause of Chronic Stercoral Appendicitis and Descending Typhlitis Colitis is discussed by H Rehder This condition was seen in Germany during the immediate postwar years (1945-48) when food shortage led

( ) Gastroenterologia 77 360 372 1951

to a diet consisting principally of vegetables (cabbage beets and potatoes) and extremely low in animal products This diet is believed to have led to an overloading of the colon with production of anatomic changes in the appendix At the same time there was actually a decrease in the incidence of classic attacks of appendicitis

Clinically there is pain in the epigastric region not in the right lower quadrant Other characteristics are epigastric discomfort feeling of fulness after meals lack of appetite weight loss irregular bowel movements and normal tempera ture Symptoms are usually present many months Bed rest generally lessens the complaints but x ray examination gives a typical picture There is no abnormality in the upper gastro-intestinal tract but a more or less pronounced funnel or trumpet shaped dilatation of the appendix is seen at its origin from the cecum with lack of demarcation from the colon Barium remains in the appendix for several weeks and even the cecum is cleared only slowly Retention in the ascending colon is seen at times

Although the condition may be chronic its course is benign without complications Appendectomy often brings no improve ment and in a third of the cases chronic typhlitis colitis persists No specific treatment has been found but bed rest fasting with a gradually increasing diet sulfonamides and careful external massage over the colon are suggested

Roentgen Findings in Ileojejunitis This is a form of chronic enteritis in which a granulomatous process similar histologically to that in terminal ileitis involves other seg ments of the small intestine Richard H Marshak A I Friedman B Wolf and B B Crohn[3] (Mount Sinai Hosp New York City) studied 49 cases of the diffuse type which from onset involves all or most of the small intestine in a continuous or interrupted pattern Symptomatology is that of a progressive disease with a gradual onset of fever weight loss abdominal pain diarrhea and on occasion incomplete obstruction An acute phase if present occurs as an exacerba tion of a long standing process The basic pathology is the same as in terminal ileitis differing only as the anatomic peculiarities of each section of bowel affect development of the disease process There is thickening of the submucosal

(3) G troente logy 19 383 408 N mbe 1951

coat by a nonspecific hyperplasia of the lymphatic tissue with round cell infiltration and obstructive lymphedema Tubercles with giant cells resembling tuberculosis but without caseation occur As mucosal ulceration progresses secondary inflammation supervenes and the granulomatous process may be obscured by diffuse inflammation and fibrosis

Roentgen features closely follow the pathologic changes



Fig 104 [illegible] (C[illegible] [illegible] Gastroenterology [illegible] 1951)

and may be divided arbitrarily into nonstenotic and stenotic forms There were 38 nonstenotic and 11 stenotic patients in this series In the nonstenotic phase the earliest mucosal changes noted were blunting flattening and thickening of the valvulae conniventes The folds were arranged in a fairly regular symmetrical parallel fashion becoming thicker irregular and partially fused (Fig 104) As ulceration proceeded one of several types of abnormal mucosal pattern was noted Cobblestoning which had the appearance of rings closely joined on a flat surface was replaced by reticulation in the

latter stage denudation of the mucosa was usually incom plete leaving behind islands of inflamed mucosa which pro duced *multiple smooth* defects of varying size Finally evident was a uniform rigid castlike tube filled with barium and showing no mucous membrane pattern These mucosal



Fg 108 —St t th se f l j j t s. Multipl a of t ct o alt at w th f d l tat on N ly ll f th mall bow l ı l d (Co t sy f M r hak R H *t al* Ga t oent l gy 19 383 408 N ember 1951)

changes were associated with local diminished mobility straightening of the loops of bowel and later rigidity of the involved segments of small intestine wide spacing of the loops and narrowing of the lumen Occasionally pseudo diverticula were noted and rarely large fingerprint like de fects simulating intramural tumors

In the stenotic phase many of the rigid loops described before became highly constricted often resembling rigid pipe

stems (Fig 105) Because of the severe narrowing there was frequent dilatation of the proximal bowel Disease might or might not be present in the dilated portions of bowel The loops were widely separated and maintained a fairly constant relation to one another The mucosal pattern was usually reticulated or castlike and skip areas of normal bowel were easily identified Both masses and fistulas were observed

Differential diagnosis usually offers no difficulty Occasionally roentgen features may be confused with changes observed in sprue lymphosarcoma and tuberculosis involving the small bowel Medical treatment is merely supportive

Clinical Effects of ACTH in Ulcerative Colitis The experience of *James A Halsted William S Adams Sol Sloan* Robert L Walters and Samuel H Bassett[4] (Los Angeles) indicates that a few patients with ulcerative colitis will have a sustained remission after ACTH therapy but that most of those benefited will relapse when treatment is discontinued Of 15 patients treated for 14-68 days after an observation period of 2 3 weeks 13 had severe long standing and 2 moderately severe disease Dosage varied but in general was the smallest amount which produced beneficial clinical effect A suggested regimen is 100 mg daily the amount being increased or decreased after about a week depending on results Nine patients showed objective signs of improvement with pronounced improvement in diarrhea while receiving ACTH Six noted *only subjective improvement* with an *improved* sense of well being and appetite but without significant effect on diarrhea Twelve had recurrence of the disease shortly after stopping ACTH 3 had remained well for 5 6 and 12 months Two of these had been severely ill for over a year before *treatment whereas the third had acute fulminating* colitis

In patients whose diarrhea and 24 hour fecal output were greatly diminished and whose stools became more solid during treatment sigmoidoscopy revealed a rapid decrease in inflammatory reaction When ACTH was discontinued and diarrhea reappeared the mucosa promptly reverted to its previously inflamed state Other effects observed during treatment included a drop in pulse rate temperature eosinophils and sedimentation rate Except for two patients the hemoglobin

(4) Gast oent l gy 19 698 721 D mbe 1951

increased to essentially normal levels in those in whom it was previously reduced There was tendency for the serum protein concentration to increase in patients in whom it was below normal initially Serious complications consisting of coronary thrombosis perforation of a duodenal ulcer and perforation of the colon occurred in three patients during therapy In an additional patient psychosis developed possibly due to cerebral edema It responded within 24 hours after ACTH was omitted coincident with a diuresis of 2700 cc

Five patients in this series also received cortisone in doses of 150 250 mg/day Results indicate that it is less effective than ACTH only one of the five showing any clinical response

The authors concluded that although ACTH cannot materially affect the bowel with irreversible damage and involvement deeper than the mucosa it may have a place in the management of chronic ulcerative colitis because of its nonspecific effects on the emotional state and improved nutrition

[Because this form of hormonal therapy produced striking relief in a number of disorders there was much hope that it would be of use in treatment of digestive tract disease To date it has proved disappointing Use of ACTH and cortisone is contraindicated in patients with chronic peptic ulcer though helpful in sprue Favorable temporary results are uniformly reported in ulcerative colitis and hormonal therapy is regarded as a valuable therapeutic adjunct but not as a cure —Ed]

Pathogenesis and Treatment of Ulcerative Colitis are discussed by Nanna Svartz (Karolinska Hosp) Typical chronic ulcerative colitis is probably of infectious origin Bacillary dysentery which is a frequent cause of an acute form of colitis with ulcerations seldom becomes chronic but after an attack of dysentery the intestine is often more susceptible to other infections Among about 400 cases of ulcerative colitis observed by Svartz chronic bacillary dysentery could be diagnosed with certainty only once Amebic dysentery rarely occurs in Sweden Bacteriologic examinations at Karolinska Hospital have revealed abundant enterococci in the feces of many ulcerative colitis patients Whether they are of etiologic significance has not been determined

Ulcerative colitis is usually insidious in onset the earliest symptom being straining on defecation Mucus at times blood tinged occasionally accompanies the stools The patient often suffers from obstipation Gradually attacks of diarrhea set in a more or less strong admixture of mucus and pus

(5) Acta m d ca d av 141 172 184 1951

becoming increasingly frequent So long as the disease is confined to the rectum and sigmoid flexure symptoms are generally mild The further it proceeds up into the intestine the more frequent is the diarrhea In children and adolescents there is a greater tendency toward upward spread even to the lower part of the ileum In such cases diarrhea is continuous *and there is often heightened sedimentation rate* emaciation tachycardia hypovitaminosis and in some cases hypoproteinemia If the inflammation penetrates deeply sepsis and hepatitis may develop X ray examinations of the intestine of 254 patients revealed total involvement of the colon in 53% Up to age 20 82% of patients showed total colon involvement between 20 and 40 38% and between 40 and 60 only 16%

The relation between ulcerative colitis and colonic cancer was studied in 290 patients treated during a 10 year period Cancer developed in nine (3 1%) Among colitis patients aged 20 or younger incidence of cancer was 4 3% Incidence of colonic cancer in the general population of Sweden is 0 02% for all ages and 0 0001% for ages 20 30 All but one patient had total involvement of the colon and in five there were also changes in the lower ileum On the basis of this material it may be advisable to subject all patients with ulcerative colitis to annual x ray examination

During five years 124 ulcerative colitis patients were treated with salicylazosulfapyridine Five died of another disease Of the other 119 90% were subsequently able to work and many of them had no further trouble Follow up five years later revealed that 84% were still capable of work None had died of ulcerative colitis

Besides sulfonamide therapy additional treatment by other methods is often indicated Blood transfusions liver and iron may be necessary in severe anemia hypoproteinemia is likewise benefited by transfusions Vitamin therapy is indicated in severe diarrhea if pellagra symptoms arise Deep ulcerations and purulent secretion in the rectum may be treated with collargol* enemas and pencilling with 0 25% collargol* Total extirpation of the colon is advisable only when other and less radical methods have failed

[Svartz is one of the more prominent continental workers in this field. The effectveness of salcylazosulfapyridine has been confirmed by others here and abroad According to Zancan *et al* of Turin (Gastroenterologia

78 34 1952) a new formaldehyde sulfathiazole compound (formo cibazol®) has been effective in many cases of infectious enterocolitis postamebic mucous colitis chronic amebic colitis and in some of idiopathic ulcerative colitis —Ed]

Treatment of Chronic Ulcerative Colitis Although conventional medical treatment should be tried in the milder forms of the disease George Crile Jr and R B Turnbull[6] recommend colectomy with simultaneous ileostomy as safest and most effective in acute toxic or severe chronic ulcerative colitis In two years they have elected the more radical procedure 22 times for chronic disease and have removed the lower sigmoid colon and rectal stump in a secondary operation in 27 patients with no deaths Rehabilitation was prompt after removal of the colon with no failure in satisfactory social adjustment after operation

Most dangerous is the acute toxic variety of ulcerative colitis found in 5% of all cases Although only 36% of patients with this form died during initial hospitalization in two to five years mortality had risen to 68% Over all mortality in patients treated by ileostomy alone or by conservative measures differed but little However only 13% of patients treated medically were rehabilitated socially and economically In primary acute toxic ulcerative colitis the colon is often atonic and distended because of invasion and destruction of both mucosal and muscular coats of the bowel Until the colon is removed blood and protein loss into the lumen of the bowel is continuous as is absorption of its toxic contents Inflammatory changes are pronounced blood vessels are thrombosed and mucosa is necrotic with deep ulceration and multiple localized areas of peritonitis Unless the bowel is removed ulceration may progress to perforation and fatal peritonitis Ileostomy alone does little more than retard this process slightly moreover fever toxemia bacteremia and a tendency to thromboembolic phenomena may persist Colectomy however removes the source of these difficulties Blood and serum protein loss is checked fever and toxemia subside serum protein content rises rapidly evidence of vitamin deficiency disappears cutaneous ulcers heal and arthritis subsides In the same two years the authors have treated the acute condition in 10 patients with ileostomy and simultaneous subtotal colectomy regardless of severity of the disease or

(6) Cleveland Cl Quart 18 239 245 October 1951

poorness of patient's condition. Two patients who died were moribund at surgery; the others improved satisfactorily. Median day of discharge from the hospital was the 13th after surgery. Several patients returned to work within a few weeks of operation—a vast improvement over the former method of treatment in which ileostomy followed by a stage colectomy required two months of hospitalization with many more months of convalescent care between stages.

As a properly made and placed ileostomy fitted with a modern appliance facilitates satisfactory social and economic adjustments, the authors see no further reason to deny patients the benefits of simultaneous ileostomy and colectomy when the disease endangers their lives or limits their social and economic activities.

[This article reflects the attitude of many American surgeons from the standpoint of surgical indication and technic. A commendable review of surgical treatment of the disease has been made by Bates (Am. J. M. Sc. 222:211, 1951). Prominent exponents of medical therapy, including Bargen, Bockus, Ricketts and Palmer, would disagree in some respects with their surgical confreres, especially with the tendency to advocate ever widening indications for operation and with the optimism over the ostomized patient experiencing protracted physical and mental comfort. Nevertheless, we may anticipate a greater resort to radical operation for this prevalent disorder, justifiable to a considerable extent by the progressive lowering of mortality and morbidity.—Ed.]

Delayed Excretion of Water with Regular Nocturnal Diuresis in Patients with Nontropical Sprue (Idiopathic Steatorrhea). Eric F. Wollaeger and Belding H. Scribner[7] (Mayo Clinic and Found.) measured urinary volume of nine patients with nontropical sprue under controlled conditions of food and fluid intake.

METHOD.—Four patients studied in a metabolism unit were fed constant high protein, low fat diet. An approximate total of 2,441 calories were in meals served at 8 a.m., 11:30 a.m. and 5:30 p.m. and in small interval feedings at 10 a.m., 3 p.m. and 8 p.m. Besides fixed fluids received with feedings, the patients drank 900 cc. water between 8 a.m. and 8 p.m. Total daily fluid intake was 3,730 cc., of which 895 cc. was in solid food. Nothing was taken between 8 p.m. and 8 a.m. Urine was collected every two to three hours during the day and as often as the patients awakened at night to urinate, usually oftener than every three hours.

Five other patients were studied with details of diet, fluid and urinary output not so well controlled, though every reasonable effort was made to do so.

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(7) Gastroenterology 19:4-41, October, 1951.

All nine patients had fatty diarrhea flatulence glossitis weight loss weakness tetany edema and hemorrhage (hypoprothrombinemia) Laboratory tests showed macrocytic anemia hypoproteinemia hypocalcemia osteoporosis small bowel deficiency pattern and flat glucose tolerance curve

Figure 106 compares volume of urine excreted by three sprue patients and three normal subjects with regulated dietary and fluid intake On this regimen patients with sprue ex-

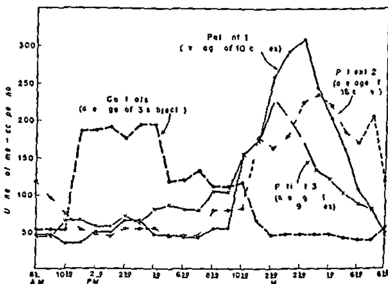


Fig 106 —Hourly volumes of urine of three patients 1 2 and 3 and of 3 normal subjects all b g e se t lly the same g l t d n tant d ly dietary nd fl d nt ke betwe n 8 m nd 8 p m (Courtesy of W llager E. E. and S rib e B H Gastroenterology 19 224 241 October 1951)

creted an average of 662 cc urine during the day and 1 936 cc at night while three normal subjects on the same program excreted an average of 1 670 cc during the day and 758 cc at night Ranges did not overlap

Patients with sprue and normal subjects were similarly studied when daily fluid intake was 1 L less The difference in day and night excretion was again apparent Some overlapping of daytime ranges was noted but none for nocturnal output Postural blood pressure studies in erect and recumbent positions were not significantly different Several patients remained at bed rest 24 hours without change in excretion

Day and night creatinine chromogen clearance tests on one patient gave similar results—further evidence that postural change with associated change in glomerular filtration rate was not responsible for the difference None of the patients showed evidence of renal disease by any test

To investigate possible relationship between impaired digestion and food absorption and delayed diuresis time of food intake was delayed four hours while time and amount of fluid intake remained unchanged When food was eaten four hours later diuresis was delayed by four hours When the evening and 8 p m feedings were omitted and no food or fluid was taken after 3 p m diuresis was again advanced several hours Varying the time when the largest portion of fluid was ingested did not affect time of diuresis

Time of diuresis was therefore related to time of food rather than of fluid intake suggesting that water excretion was delayed by retention in the intestinal tract during the abnormally long time required by the malfunctioning bowel to digest and absorb food Fluid given intravenously in fasting state caused immediate diuresis but when given after breakfast urine was not passed in large amounts until that night The absence of diuresis can be explained by entrance of fluid into the alimentary tract in response to the presence of food

In another study nocturnal diuresis did not take place if the patient fasted all day but ingested the same amount of fluid Urinary excretion then resembled that in normal individuals Moreover that patients with sprue have an optimal need for water in the small intestine was indicated since in lower ranges of fluid intake increase in fluid caused increase in night urine but little change in urine during the day When fluid intake was increased beyond a certain point however night urine did not increase further but day urine did

The fact that daytime diuresis could be induced both during fasting and with large fluid intake after food ingestion is evidence that retention of fluid by body tissues was not the primary cause of nocturnal diuresis It is suggested that fluid retention in the small bowel of patients with nontropical sprue is as much a compensatory phenomenon by means of which food is kept dilute and absorption facilitated as is the obligate excretion of excessive dilute urine by diseased kidneys

Patients with sprue may give a false positive result with the Kepler water test for Addison's disease as a result of this aberrant fluid utilization

Studies on Effects of Cortisone and Pituitary Adrenocorticotrophic Hormone (ACTH) in Sprue Syndrome Use of these hormones appeared justified because of their well known effects on appetite and subjective well being Even in the absence of a specific effect on intestinal absorption this could favorably affect the therapy resistant patient with primary sprue

David Adlersberg Henry Colcher and Stanley R Drachman[8] (Mount Sinai Hosp New York City) administered ACTH (five courses) and/or cortisone (eight courses) to five patients with the typical clinical chemical and roentgenologic picture of primary sprue Before hormonal treatment four had proved resistant to conventional therapy Four patients received ACTH intramuscularly every six to eight hours in equally divided doses totaling 50 100 mg/day A total dose of 500 1 950 mg/course was administered over five days to four weeks The five patients given cortisone received a total dose/course of 500-4 500 mg over 5 77 days In five courses the hormone was given intramuscularly and in three orally The initial daily dose was 100 mg this was gradually reduced to 50 mg The hormone was given either once a day or in two equally divided doses every 12 hours During both ACTH and cortisone therapy patients were continued on the therapeutic regimen given previously which included administration of liver extract and/or vitamin B_{12} and folic acid

Both ACTH and cortisone produced a clinical and symptomatic response in all patients treated Appetite increased there was an improved sense of well being and diarrhea disappeared During short courses body weight fluctuated however considerable weight gains (up to 43 lb) were noted after prolonged cortisone therapy Although steatorrhea persisted quantity of fecal fat in stools often decreased considerably or was at times normal for varying periods In two courses of ACTH therapy and one of cortisone special tolerance tests performed with standard doses of vitamin A revealed direct effects on intestinal absorption Occasionally

(8) Ga t oe t logy 19 6 4 697 D mbe 1951

serum carotene and serum albumin levels were increased over pretreatment levels Improved absorption of fat was associated with higher serum calcium levels in some patients Nevertheless in two instances hormonal therapy had to be reduced or temporarily discontinued because of appearance of manifest tetany which was precipitated by presence of hypocalcemia and development of hypochloremic alkalosis In patients with sprue especially those with hypocalcemia additional quantities of calcium gluconate and potassium chloride should be given from the start of hormonal therapy Hematologic results could not be evaluated in these patients because most of them continued to receive antianemic therapy Therapeutic results depended on duration of administration and varied from patient to patient After cessation of therapy remission could be maintained for short periods only despite uninterrupted administration of liver extract vitamin B_{12} and/or folic acid

Although results of this study are limited by the small number of patients who were observed for relatively short periods they seem to justify additional trials of ACTH and cortisone in patients resistant to accepted therapy

[These results are confirmed by the observations of Taylor Wollaeger and Comfort (Gastroenterology 20 703 1952) on six patients with nontropical sprue treated with cortisone They concluded that to date cortisone offers the most effective means of treating this disorder in exacerbation However its effectiveness in long term management remains to be evaluated —Ed]

Multiple Polyposis Results of Fulguration of Polyps in Distal Portion of Colon after Ileosigmoidostomy and Colectomy in 27 cases indicate that the patient has a more normal existence and outlook with this treatment than with ileostomy according to Newton D Smith and John R Hill[9] (Mayo Clinic) Fulguration was usually done daily using monopolar or Oudin current through the regular 25 cm Buie sigmoidoscope with an auxiliary suction tube to remove smoke The fulgurating electrode is not applied directly to the polyp but there is an intervening spark gap of 3 7 mm (Fig 107) By beginning at the anus and fulgurating proximally the surgeon is able to observe the previously treated area and the patient seems to learn to co operate more satisfactorily The general purpose has been to clear the bowel of polyps just before or soon after operation The distal portion of the colon is then

(9) J A M A 148 440 443 Feb 9 1952

examined every three months for two or three times then at six month and one year intervals These periodic examinations are necessary for optimal results

Symptoms observed before treatment included bleeding in 24 patients diarrhea in 21 abdominal cramps in 11 and constipation in 3 Age at onset varied from the first to the fifth decade Two patients died of bronchial pneumonia soon after operation and two more died five and eight years after treatment was instituted of causes other than multiple polyposis There were two deaths from carcinoma both in the same

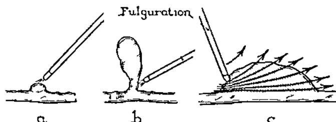


Fig 10 —Method and site of application of spark of fulgurating electrode to (a) small sessile polyp (b) pedunculated polyp and (c) large sessile polyp (Courtesy of Smith N D and Hill J R J A M A 148 440 443 Feb 9 1952)

family one 2 years and the other 34 months after operation Malignancy had been noted in the first patient at the time the colon was excised the other patient postponed colectomy too long although she had often been urged to have the operation The fact that other members of the same family in preceding generations died of carcinoma of the colon at about the same age or within the next decade suggests in this family a hereditary age relationship between development of carcinoma and presence of multiple polyposis The other 21 patients were living and apparently working without appreciable handicap 6-19 years after treatment

The use of antibiotics and the increased understanding of surgical problems have reduced postoperative mortality and morbidity in these patients The study should be continued

Important Clinical Dividends from X ray Examination of Colon. Fred J Hodges and Howard C MacMillan[1] reviewed results of 15 350 colon examinations representing 7 2% of

(1) J A M A 147 1191 1194 N 24 1951

over 200 000 diagnostic x ray examinations performed during 1944–49 at the University of Michigan Though findings were considered within normal range in 71 7% negative findings which serve to decrease the number of differential diagnoses are truly valuable

About 25% of all patients showed some abnormality the commonest being diverticulosis mainly in the upper sigmoid Though usually a bland insignificant condition proof of its existence is valuable especially when associated with in

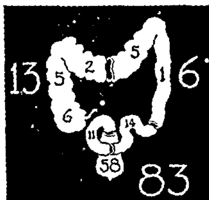


Fig 108 – Lo t on of 102 malg t l t mor (Cou t y f Hodge F J and M M ll n H C J A M A 147 1191 1194 N v 4 1951)

flammatory disease of the intestinal wall X ray investigation is helpful in initial diagnosis evaluation and treatment of ulcerative colitis

During one of the five years reviewed 131 primary large bowel neoplasms were recorded of which 102 were verified *The distribution is shown in Figure 108* Of initial symptoms recalled change in bowel habit (48%) blood in stool (43%) and abdominal pain (20 %) singly or in combination were the most frequent The most effective methods of physical examination were sigmoidoscopy positive in 68 6% and rectal examination positive in 56% of the entire group In the 102 cases only one lesion was missed on x ray examination Subsequent review of the film showed it almost completely hidden by superimposition on the descending colon The error

was inexcusable because examination should not have been considered satisfactory until all intestinal segments had been adequately seen

X ray methods should be used as an adjunct even in rectal tumors accessible from the exterior so that status of the colon above may be determined before treatment Above the midsigmoid the main burden of detection and correct diagnosis rests with x ray study The more reliable symptoms and physical signs are found in cases in which direct examination through the rectum is most effective

METABOLISM

ROBERT H. WILLIAMS M.D

PART VI

METABOLISM

DIABETES AND HYPERINSULINISM

Assays for insulin in the pancreas and in blood of diabetics have demonstrated a subnormal content of insulin The younger and more severe diabetics t nd to have lower values than the others

NPH insulin has been shown in many clinics to be one of the most useful preparations

Pregnancy liver extracts in preliminary studies show promise in the treatment of diabetic neuropathy —Ed

Endocrine Control of Blood Sugar mediated through the intestinal tract liver kidneys and tissues is summarized by C N H Long[1] (Yale Univ) Rate of absorption from the intestinal tract depends on metabolic rate of tissues and composition of diet but not glucose concentration

In the liver glycogenolysis is accelerated by epinephrine and the hyperglycemic factor of the pancreas Gluconeogenesis is controlled by the adrenal cortical hormones Glycogen formation depends on the amount of available insulin Maximal renal absorptive capacity increases in hyperthyroidism but decreases with administration of adrenal steroids Tissues utilize glucose by transforming it into glycogen by oxidizing it to carbon dioxide and water and by forming fatty acid

The upper limit of blood glucose level is largely determined by insulin secretion since it determines rate of utilization of glucose in the tissues On the other hand maintenance of a minimal blood glucose level results from a complex interplay between anterior pituitary secretions adrenal cortical hormone and in some instances the hormone of the adrenal medulla This interplay maintains blood glucose level in three ways (1) discharge of epinephrine makes available any preformed liver glycogen (2) the release of ACTH augments secretion of the 11 oxygenated adrenal steroids one of whose functions is to accelerate the formation of glucose from non carbohydrate precursors and (3) suppression by these steroids

(1) Lan s 1 325 1 9 Feb 16 1952

of carbohydrate utilization by tissues In this they may be reinforced by the anterior pituitary growth hormone or possibly by another still unidentified hormone from this gland

[As indicated many factors are concerned with the regulation of carbohydrate metabolism gastrointestinal tract liver kidney pancreas, pituitary adrenal etc The pituitary antagonizes the action of insulin by means of ACTH growth hormone and possibly a specific anti insulin principle these pituitary substances are diabetogenic Indeed there have been many instances of frank diabetes at least transiently in patients given ACTH therapy this occurs chiefly in individuals with a family history of diabetes —Ed]

Extractable Insulin of Pancreas Correlation with Pathologic and Clinical Findings in Diabetic and Nondiabetic Cases is presented by Gerald A Wrenshall A Bogoch and R C Ritchie[2] (Univ of Toronto) Of 213 subjects 139 were nondiabetic 68 of them under age 10 at death Of the rest 64 were diabetic and 10 possibly diabetic

The following conclusions were reached for nondiabetic subjects (1) Extractable insulin of pancreas in hospitalized adults did not change with interval between death and autopsy or with days of confinement to bed preceding death Concentration was slightly higher in hospitalized than in sudden death subjects (2) Concentration of extractable insulin of human pancreas is lowest in the head and highest in the tail portion (3) Trends for age indicate that it increases in passing from prematurity through birth with a maximum level at age 6 months This is followed by a shallow minimum at age 3 Thereafter extractable insulin rises continuously to adult level between ages 12 and 17 Trends less pronounced after this age consist of a slow decrease with advancing years with probable maximum in the fifth decade of life (4) Concentration of extractable insulin increases progressively with decreasing pancreatic weight in adults (5) Cause of death had little effect on the value for extractable insulin

The following conclusions were reached for diabetic subjects (1) Diabetes mellitus patients have lower average extractable insulin than controls who die of the same assigned cause In the growth onset type of diabetes extractable insulin of pancreas was extremely low it was much higher in the maturity onset type (2) In eight instances of diabetic coma extractable insulin was extremely low (3) Little correlation could be found for duration of diabetes prolonged

(2) D bet 1 87 107 Mar Ap 1952

hyperglycemia or type of therapy in maturity onset type of diabetes (4) Perhaps the characteristic atrophy of the islets of Langerhans and extremely low values for extractable insulin at autopsy in growth onset type of diabetes may be related to the simultaneous hyperglycemia and factors promoting active growth The insulin blockage hypothesis in the maturity-onset type of diabetes requires further study

[The decrease in insulin content of pancreas of diabetic subjects with maximal deficiency in the young group is somewhat in accord with the low plasma insulin content described in the next article —Ed]

Plasma Insulin in Human Diabetes Mellitus was measured by J Bornstein and R D Lawrence[3] (London) in 37 diabetics and 14 normal controls Available plasma insulin is measured by injecting 1 ml plasma into special rats and observing change in the blood sugar for one hour The rats are first made diabetic with an appropriate dose of alloxan Then the hypophysis and both adrenals are removed so that the animals become highly sensitive to insulin and show a clear hypoglycemic effect after even 1/20 000 of a unit

As a result of this study the authors classify human diabetes into two main types The first is severe characterized by weight loss and ketosis as well as hyperglycemia it is seen at any age but mainly in the young the plasma contains no available insulin but when injected in rats makes them insensitive to subsequent insulin injections Such patients require insulin treatment to live The second type is that of middle aged obese individuals it differs in that there is no ketosis or weight loss The plasma contains available insulin (about 70% of normal) but does not cause insensitivity to insulin in rats The diabetic state is easily controlled solely by diet especially if obesity is thereby reduced

[For many years two general types of diabetes mellitus have been described The marked difference in plasma insulin helps explain some of the differences in the course of disease in the two groups

In other studies the serum has been shown to possess substances that were antagonistic to insulin this phenomenon being greatest in patients with pronounced insulin resistance Such observations prompt more consideration as to how much a role insulin inactivation plays in the pathogenesis of diabetes —Ed]

Symposium on Blood Glucose Surveys in hospitals throughout the United States to check accuracy of some of the more common chemical measurements have revealed a high degree of unreliability As diagnosis and treatment of

(3) B t. M J 2 1541 1544 Dec 29 1951

diabetes largely depend on blood glucose measurements the importance of reliable trustworthy methods in clinical laboratories cannot be overemphasized

In the opinion of F William Sunderman Robert P MacFate Gerald T Evans and John B Fuller[4] a modified Benedict method is best It is simple accurate and relatively specific for glucose it is economic of material time saving and nonhazardous to technical staff

Regardless of method employed to measure blood glucose levels error must be guarded against by avoiding dirty glass ware incorrect reagents incorrect test technic and incorrect calculations One of the commonest sources of error is in the blood sample itself (1) it may have been drawn after a meal or (2) stood too long so that glycolysis has taken place (3) it may contain an excess of anticoagulant or (4) double oxalate (used for sedimentation rate) which contains ammonium oxalate and cannot therefore be used for glucose measurement

No reagent entirely specific for glucose has been developed All known glucose reagents are somewhat affected by the saccharoids—the nonglucose nonfermentable reducing substances in blood Among these saccharoids are creatinine acetone glutathione and diacetic glucuronic uric and ascorbic acids Saccharoid errors of 30 50 mg /100 ml in glucose equivalents have been found with some reagents the error with the Benedict reagent is 5 6 mg /100 ml in glucose equivalents Since most saccharoids in blood are in red cells closer to true glucose values are obtained if less hemolysis is allowed in preparing the filtrate values

[For precise interpretations of blood glucose values one must use a method that is precise and does not include varying quantities of saccharoids —*Ed*]

Method of Increasing Sensitivity of Glucose Tolerance Test Herbert Berger (Staten Island N Y) reasoned that as cortisone is so diabetogenic it might serve to increase sensitivity of the glucose tolerance test thereby facilitating earlier detection of potential diabetics

Two glucose tolerance tests were given to 50 patients the first using usual technic and the second identical except that the patient was given 100 mg corticotrophin one hour

(4) Am J Clin Path 21 901 934 October 1951
(5) J A M A 148 364 368 Feb 1952

before the test In the corticotrophin test failure of the blood sugar to return to normal in three hours and/or an increase in intermediate blood sugar measures over figures obtained in the control test was considered positive result The test showed positive results in 12 known diabetics and in 14 sib lings of known diabetics and negative results in all but 1 of 18 patients all over 50 without diabetes or diabetic family history of 6 normal persons under 30 1 had positive results in that intermediate blood sugar values were all higher with corticotrophin whereas the three hour sample was normal

Results suggest that corticotrophin may increase sensi tivity of the glucose tolerance test Follow up after 5 10 years will prove or disprove this point

Use and Abuse of Dextrose Tolerance Test. Samuel Soskin[6] (Michael Reese Hosp) believes this test should be considered an index not of ability to oxidize carbohydrate but rather of efficiency of blood sugar utilization by the liver under various endocrine influences The blood sugar level is not greatly different when a person rests in bed or exercises vigorously yet the rate of utilization of carbohydrate in these situations varies greatly Normally blood sugar content is disturbed only for an hour or two after enough sugar is taken in to last 6-12 hours Part of this intake is used and part stored In the glucose tolerance test the glucose is regulated by the liver and utilization and glycogen storage are increased Of these Soskin believes hepatic regulation to be the most im portant In depancreatized animals given sufficient insulin to maintain a normal blood sugar level additional glucose ad ministration evokes a normal tolerance curve Extra secretion of insulin is not needed On the other hand hepatectomized animals given a constant infusion of glucose sufficient to maintain normal blood glucose levels have no deficiency of the pancreas or of utilization by peripheral tissues Neverthe less additional dextrose to such animals results in a diabetic type of tolerance curve The liver is needed to adjust the output of glucose Direct measurements of blood glucose and liver blood flow have shown the regulation of the liver to be like that of a thermostat The blood sugar is itself the stimulus for regulation When it rises above normal level the liver stops putting out sugar As soon as the extra sugar is used up

(6) Postg ad M d 10 108 116 A gu t, 1951

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(4) Am J Cl n P th 21 901 934 October 1951
(5) J A M A 148 364 368 F b 2 195

globin or NPH insulin that has maximal effect during the daytime should be given instead of PZI to avoid the risk of a hypoglycemic reaction early in the morning

If an intermediately acting insulin is used and the diet divided into three equal meals each taken in toto at regular mealtimes two handicaps occur First the breakfast is too large to permit good control during the forenoon since intermediately acting insulins require several hours before they reach a high degree of effectiveness Second if supplementary

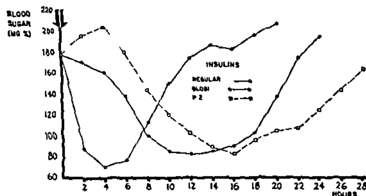


Fig 109 —C mpa i ffect of d t cal dos (60 u ts) f g) glob n d p t m e i l wh adm t d b t u ly t hype gly m p t t wh v d 0 Gm ca b hyd ate o lly y tw h d g the b t on pe od (C t y f D n an G G M t b l m 1 101 110 M h 1952)

nourishment is not given in the late afternoon between 3 and 4 30 p m it may be impossible to use the amount necessary to carry the desired effect through the evening and night without danger of provoking hypoglycemia before supper when the effect of the insulin is greatest Both handicaps are eliminated if after the diet is divided into three equal meals a bread and milk exchange is extracted from the breakfast and given between 3 and 4 30 p m This measure is often the only difference between succe s and failure in satisfactory control by means of a single daily injection of a single insulin Similarly if a single dose of regular insulin is given with PZI (as a mixture) before breakfast an effective plan is to remove a bread and milk exchange from the luncheon for a bedtime snack to prevent hypoglycemic reactions during

and the level falls below normal the liver starts to put out glucose again Insulin and anterior pituitary adrenal cortical and thyroid hormones set the level of the regulating mecha nism The chief forces are the hormones of the anterior pituitary and pancreas acting in different directions Increased insulin or decreased pituitary hormone leads to hypoglycemia the reverse leads to hyperglycemia

The oral glucose tolerance test is unreliable because it depends on the rate of gastrointestinal absorption of sugar, influenced by the same endocrine glands having to do with regulation of blood sugar level The flat curve of oral dex trose tolerance test in hypopituitarism indicates only that absorption of glucose is slowed When the test dose is ad ministered intravenously in the same patient a normal curve is obtained Liver dysfunction on the other hand interferes notably with the glucose tolerance test Elevated fasting levels of glucose in the blood may also be produced by liver disease whereas in mild diabetes fasting glucose blood levels may be normal Soskin believes the oral dextrose tolerance test as ordinarily used and interpreted is practically worthless To avoid the variations due to absorption he gives 50% glucose intravenously 0 3 Cm./kg body weight Normally the blood sugar after such a test returns to normal in 60 minutes and the diabetic curve after 120 180 minutes With liver disease normal values are obtained between 60 and 120 minutes

[This is a good evaluation of the pertin nt rol of the liver in carbohydrate metabolism with its effect on blood sugar values —Ed.]

Practical Use of Various Insulins in Management of Diabetes Mellitus The potential for confusion has been in creased with the advent of multiple insulins and the various mixtures Failure to abandon measures made obsolete by new discoveries adds to the confusion The widespread continued use of protamine zinc insulin (PZI) as the only insulin is an example The continued manufacture of crystalline insulin the effectiveness of which is indistinguishable from that of regular insulin must confuse many Garfield G Duncan[7] (Jefferson Med College) has abandoned the solitary use of PZI If the diabetes is so mild that the slow action of a single dose of PZI is adequate during the daytime a small dose of either

(7) Met bol m 1 101 110 Mar b 1952

of the respiratory tract there is usually no need to change the plan of insulin therapy When this is not entirely satisfactory and the complication is going to have a short course the precomplication scheme of therapy is maintained but superimposed on it is administration of regular insulin every four or six hours The doses are regulated in a manner aimed at controlling the glycosuria and when the fever subsides the superimposed regular insulin is discontinued and suitable increases in the basic insulin are made For the more serious and prolonged complications the diet is divided into four equal meals given every six hours and with regular insulin—to the exclusion of other insulins—administered before each feeding The dosage based on degree of glycosuria is increased rapidly until good control is achieved care being taken to reduce the amounts given with equal rapidity with the abrupt subsidence of the acute complication Except in cases of profound resistance to insulin regular insulin can be relied on to control the hyperglycemia for six hours if enough is given

[The many therapi s have been confusing to physicians as well as patients Two in ulin preparations alone or comb ned are satisfactory for most patients regular or crystalline NPH or globin Readjustments in temporal distribution of quality and quantity of d ets hould be utilized often

Simplification in the therapeutic armamentarium should al o include reduction in the types of syringes di pen ed

Of course with intelligent patient various readjustments in care may be inst tuted as further described in the following article —Ed]

Use of Mixtures of NPH and Unmodified Insulins was studied by John W Stephens Robert M Donaldson Jr and Alexander Marble[8] (New England Deaconess Hosp) Multiple blood sugar studies were made on 23 boy campers receiving NPH insulin alone or combined with regular insulin either as separate injections or as mixtures in one syringe Results indicated that the single syringe technic is as satisfactory as separate injections when both insulin forms are required to offset significant hyperglycemia after breakfast

Diabetic Acidosis Results of Treatment in 67 Consecutive Cases Reed Harwood[9] (Massachusetts Gen l Hosp) reviewed the records of all ward patients with severe or moderately severe diabetic acidosis admitted in 1944-50 except

(8) A M A A h I t M d 88 356 361 S pt mb 1951
(9) N w E gl d J M d 245 1 9 J ly 5 1951

the night Extensive clinical trials over long periods have proved the value of these changes They have been based on duration and degree of effectiveness of the relative insulins (Fig 109)

All patients in whom diabetes is not satisfactorily controlled when the appropriate diet is adhered to and body weight is at the desired level should receive insulin Also irrespective of body weight all patients should be given insulin when they have acute febrile complications or other complications that tend to disturb control of the diabetes Obese patients should not receive insulin except when they have such complications The thin diabetic and the child diabetic have severe diabetes and must always take insulin they must have insulin even when body mass is below normal When their weight is increased an increased need for insulin ensues All grades of severity of diabetes occur between these two extremes

In good control of diabetes all but the occasional blood sugar value recorded monthly should be below 140 mg/100 cc fasting and below 180 mg within two hours after a meal Glycosuria should be prevented when practicable but small amounts of sugar in urine are preferable in labile diabetes to the risks of having hypoglycemic reactions Over 70% of the author s patients requiring hospitalization for complications come from that smaller group who do much as they please

Three plans which suffice to control diabetes in the absence of acute complications are recommended (1) a single dose of globin or NPH insulin given 1 hour before breakfast daily (2) a mixture of NPH and regular insulin given 15 minutes before breakfast daily (3) a mixture of NPH and regular insulin given 15 minutes before breakfast daily and a small dose of NPH insulin given immediately before or immediately after supper One dose of globin or NPH insulin usually suffices for the patients whose diabetes falls between that of the overweight patient requiring no insulin and severe labile diabetes The undernourished diabetic who has severe diabetes is given a mixture of NPH and regular insulin before breakfast if this fails an additional small dose of NPH insulin is given at supper

For mild complications such as acute but minor infections

tion It is in those patients receiving additional glucose that a critical potassium deficiency develops during therapy The possibility of potassium intoxication is avoided by delaying replacement therapy beyond that initial period when the serum levels are already high and by avoiding potassium administration in the presence of oliguria or severe renal damage Buffered phosphate was given for continued stupor but results were not remarkable When indicated whole blood and plasma were given

The initial dose of insulin was 50 200 units with additional doses (100 200 units in the more severe cases) given every ½ 1 hour depending on the blood sugar response When control was evident dosage was reduced and the interval lengthened until administration was stopped at a blood sugar level of 200 mg /100 cc Average total dose in the first 24 hours was 1 260 units Ample doses were given in the belief that diabetic acidosis is a state of acute insulin deficiency in which resistance to the effects of insulin grow as its administration is delayed Only eight instances of hypoglycemia occurred Each patient received nourishment orally as soon as possible Gastric lavage penicillin and indwelling catheters were used as indicated

Importance of Life Stress in Course and Management of Diabetes Mellitus Lawrence E Hinkle Jr and Stewart Wolf[1] (Cornell Univ) studied diabetic patients under experimental stress by abruptly discussing suspected topics of conflicts The usual initial reaction of a fasting diabetic to conflict was transient fall in the blood glucose level accompanied by rise in ketonemia If the stress was continued the blood glucose level ceased to fall and sometimes rose In labile diabetics in the fasting state the initial fall during stress was sometimes large enough to precipitate hypoglycemic symptoms On the other hand in fasting persons suddenly made very fearful or angry a rapid rise in the blood sugar level apparently as a result of secretion of epinephrine often developed Moreover situations associated with loneliness sadness and resentment were sometimes associated with a more diabetic glucose tolerance curve When a diabetic with a relatively high blood glucose level and established glycosuria is placed in a conflict situation his reaction may

(1) J A M A 148 513 520 F b 16 1952

those in the pediatric service Of 57 patients hospitalized 67 times all but 6 had a serum carbon dioxide content of less than 10 mEq/L Infection and long continued neglect of the diabetic regimen were the commonest causes of acidosis One third had not taken insulin for one to three days before hospitalization Previously undiagnosed diabetes existed in 13 Only one patient was completely unconscious but several lapsed into coma soon after admission In most diastolic blood pressure was depressed usually being 60 85 mm Hg Absence of coma and shock however does not assure a favorable outcome The one patient who died had renal failure probably unrelated to diabetes

Correlation of severity of the acidosis with height of the blood sugar level was better than with depression of the serum carbon dioxide content Both blood sugar and carbon dioxide levels tended to return to normal in the first few hours the former being essentially normal in 12 18 hours and the latter in 5 20 hours When considerable amounts of glucose were given intravenously the blood sugar level declined more slowly patients so treated seemed to respond less well than those who received little or no glucose Blood nonprotein nitrogen tended to be elevated in the more serious cases Serum sodium and chloride levels were generally low whereas potassium and phosphorus levels tended to be elevated on hospitalization and to fall below normal with therapy

During the 5½ year period early intravenous fluid therapy was changed from use of normal saline solution with either sodium lactate or bicarbonate to use of a solution with lesser concentrations of sodium and chloride and with added potassium and phosphate The solution contained 2 2 Gm sodium lactate 0 6 Gm sodium chloride 1 Gm potassium chloride 0 5 Gm potassium dibasic phosphate and 1 000 cc of 5 10% glucose solution The concentrations per liter were 30 mEq sodium 20 mEq potassium 23 mEq chloride 20 mEq lactate and 90 mg phosphorus With such a solution potassium and phosphate deficits are corrected most easily and the dangers of giving excessive sodium in the presence of potassium deficit are avoided Because glucose in water was used as a diluent (hospital rules forbade distilled water on the wards) blood sugar levels rose after administra

with incidence of such complications James Lee Wilson Howard F Root and Alexander Marble[2] (New England Deaconess Hosp) studied 247 diabetics in whom the disease developed between age 18 months and 50 years and duration was 10 34 years

Degree of control was excellent in 2.8% good in 12 1% fair in 20 7% and poor in 64 4% Criteria for excellent control included absence of coma initiation of insulin therapy a few weeks after onset of diabetes urine tested more than once daily with a conscientious attempt to have it aglycosuric or nearly so before meals diet weighed at least 80% of the time since onset of diabetes and physical examination with satisfactory blood and urine tests at least once annually Good control standards were the same as for excellent with a few exceptions Coma was never present except when diagnosis was made in coma and diet was weighed for the first six weeks of treatment and at intervals thereafter with careful measurement at other times Fair control standards were no coma except when diagnosis was made in coma or coma was precipitated by unavoidable overwhelming infection or other complication insulin therapy begun within 24 months of onset urine tested one or more times weekly conscientious diet control without weighing or measuring and satisfactory blood sugar values and physical examination at least once in two years Poor control was designated when there was avoidable coma one or more times insulin therapy was begun over 24 months after onset of symptoms and there was no correlation of diet insulin and urine tests or regular examinations Complications were evaluated by urinalysis phenolsulfonphthalein excretion electrocardiogram capillary fragility tests ophthalmologic examinations with tonometry visual field and acuity tests slit lamp examination and funduscopy with dilated pupils and x ray examination of pelvis lower legs and abdominal aorta for vascular calcifications Calcification was classified as minimal (one or more small flecks of calcium in linear arrangement in one or two small areas not over 2 cm long) moderate (tiny linear calcifications over 1 or 2 cm long in one or more arteries) or marked (dense calcification)

(2) Am J M Sc 1 479 489 May 1915

include rapid rise in blood ketones and greatly increased excretion of water glucose ketones and chlorides In short term experiments the authors observed a rise in blood ketones of 19 mg /100 cc in 1½ hours and excretion of as much as 4 7 cc water/minute (282 cc /hour) 490 mg glucose/minute (29 4 Gm /hour) and 25 2 mg chloride/minute (1 5 Gm /hour) In a setting of stress a diabetic may excrete enough glucose to deplete the glycogen stores rapidly and at the same time may lose large amounts of chloride and fixed base Metabolic changes in diabetics in response to stressful life experiences may sometimes be of great magnitude and they may have serious consequences if not promptly counteracted

Study of the life histories and daily experiences of diabetics indicated that many of the apparently spontaneous fluctuations in the syndrome were the results of life stress The similarities in the life histories of these diabetics suggested that developmental cultural and psychologic factors may have an important influence on onset and course of the disease Their behavior under stress attitudes toward food and feelings toward their parents were often so similar as to suggest that these psychologic manifestations might be considered as symptoms of the total disease process Treatment directed at alteration of the patient s behavior and attitudes and of his relation to his environment aided prevention of otherwise uncontrollable fluctuations in the course of labile diabetes and recurrent episodes of ketosis requiring hospitalization

[Undoubtedly the emotional factors pre ent a real problem in the regulation of some diabetics —Ed]

Prevention of Degenerative Vascular Lesions in Young Patients by Control of Diabetes The high incidence of premature vascular disease in diabetes of long duration has been felt by some to be inevitable these advocate management in which free diet is allowed and insulin used only to combat acidosis Glycosuria and hyperglycemia are thought to be unimportant in such a program Others believe that restoration of physiologic conditions including aglycosuria and normal blood sugar will aid in prevention of degenerative complications To compare degree of control

showed good to excellent results and 10% had a fair result In some patients evidence of improvement was manifested within two hours In those who had good to excellent results remission in the clinical symptoms occurred within a week after institution of treatment The objective manifestations of reversibility were not as striking as the subjective Although improvement in vibratory sense could be detected quantitatively this first became evident two to four weeks after therapy was started Disturbances in tendon reflexes and muscle atrophies seemed irreversible Patients in whom diarrhea was an outstanding manifestation of visceral neuropathy and in whom no organic basis for this symptom could be established were relieved within a week

The effects were probably due to components not previously isolated from liver Failure of this extract to cause reticulocytosis is presumptive evidence that its antineuritic properties are not ascribable to vitamin B_1 or folic acid Furthermore analysis revealed presence of only 0 09 μg vitamin B_{12}/ml and 0 15 μg folic acid/ml

[These prelim nary studies are sufficiently promising to warrant their continuation The results are distinctly b tter than those reported with corti one vitamins and other ag nt —Ed]

Encephalopathy of Hyperinsulinism may be temporary or permanent S K Fineberg and Alexander Altschul[5] (Harlem Hosp) consider hyperinsulinism to be that state produced by excessive insulin of either exogenous or endogenous origin They believe this term preferable to insulin shock which is inaccurate and misleading The disturbance of brain function in hyperinsulinism may be profound It may mimic psychosis as in the case reported here

Woman 31 known to have diabetes mellitus for 10 years was found in coma Muscle twitchings were present in the arms and legs After administration of 50 cc of 50% glucose intravenously followed by 1 000 cc of 10% glucose in distilled water she gradually revived Coma la ted for more than 24 hours When conscious she was lethargic irrational and completely disoriented She was totally incontinent of urine and fece This state persisted for 10 days Even a month after admission she was withdrawn and melancholic and would become enraged without provocation

In another patient coma persisted for 19 days with severe and variable neurologic signs A year after hospitalization she was totally dependent on others understanding was ade

(5) A I t M d 36 536 550 F b ry 1952

Degree of calcification correlated well with degree of fundal change Of 37 patients with better than fair control only 9 had *moderate calcification* and 7 *moderate retinitis* none had marked changes by *either measurement* Of 159 patients with poor control 70 had moderate to marked calcification and 86 a similar degree of retinitis

In patients with good or excellent control advanced calcification marked retinitis or diabetic nephropathy was not *found even after 20 years of diabetes* Three of the 4 patients with *excellent control after 20 years had no retinal lesions* whereas of 54 with moderate to marked retinitis only 5 had good and none had excellent control

It was found that 63% of patients with good or excellent control but only 38% of those with poor or fair control lived long enough to be in the group having had diabetes *20 or more years* The *authors concluded that the specific factors* causing degenerative lesions in diabetics are controlled by regulation of the disease

[This is just one of many reports showing the rewards for good control of diabetes —Ed]

New Liver Extract Derived from Pregnant Mammalian Liver I Its Effect on Peripheral Neuropathy William S Collens James D Zilinsky Jerome J Greenwald and Arthur B Stern[3] (Maimonides Hosp Brooklyn) found that crude *liver extract was of value in diabetic neuropathies* Most effective was a special pregnant mammalian liver extract The extract was given to 127 diabetic patients with neuropathies manifested by peripheral numbness tingling sticking pains pins and needles sensations drawing pains in the legs *burning sensations in the toes or feet stiffness in the extremities* and burning tongue They also had symptoms due to effects on the central nervous system such as crying spells depressions agitation and vertigo Those symptoms of visceral neuropathy related to involvement of the autonomic nervous system *included anorexia belching diarrhea* and urinary incontinence Treatment consisted of intramuscular injection of 5 cc pregnant mammalian liver extract daily in most cases injections were continued for two weeks Care was taken to eliminate suggestion in evaluation of *results*

In *94% of patients reversal of symptoms* was noted 84%

(3) Am J M Sc 12 53 58 Jan ary 1952



F g 110—R ght foot. \ t d ru t h g ta sal bon Ch g adj ce t p t f met t l t b d fib l t s ly th w (Co t y I B dl m n B and D G G Am J M d 12 435 J n ary 1952)

athy (Fig 110) and (2) rarefaction of the phalanges and *metatarsals secondary to chronic infection in the adjacent* soft tissues and arterial insufficiency

Fatigue States Associated with Abnormal Carbohydrate Metabolism may be due to the inability of certain persons *to respond normally to an excess of stimulation* G A Cronk[6] *(Syracuse Univ) studied 45 patients with such syndromes* The histories are almost always the same After a period of fairly normal environmental adaptation the patient encounters unusual stress (college life in these patients) Fatigue develops insidiously and is not overcome by normal periods of sleep Unpleasant environmental activities aggravate the con

(6) Jou al Lan et 71 484-487 N embe 1951

quate but orientation poor There were aphasia right mono paresis and bilateral Babinski signs Two other patients died as a result of brain damage due to hyperinsulinism Autopsy on one showed diffuse cellular changes throughout the brain A fifth patient aged 15 had had diabetes mellitus since age 7 and had never been well controlled In one episode she was comatose for 72 hours and in the posthypoglycemic phase had Babinski signs and other signs of neurologic in volvement These had cleared by the time of discharge and an electroencephalogram a year later was normal In the three years after discharge she was readmitted 12 times but she has never shown deficiency or impairment of mentality

Encephalopathy from hyperinsulinism depends on an in sufficiency of glucose in the brain There may also be some direct toxic effect of insulin in the brain when the blood sugar is low It appears worth while to consider use of the insulin antagonistic pituitary adenocorticotrophic hormone (ACTH) and adrenocortical hormones in hyperinsulinism if encephalopathy and coma do not respond to glucose ad ministration

[The authors emphasis on the brain damage produced by severe hyper insulinism is quite appropriate Hyperinsulinism particularly the func tional type is far more common than is generally recognized. The 48 hour fast is distinctly the best test for islet adenoma it rarely fails to induce hypoglycemia —Ed]

Charcot Joints and Infectious Vascular Lesions of Bones in Diabetes Mellitus Only 27 cases of this complication have been reported Typically the patients have had poorly con trolled diabetes for many years with gradual development of severe neuropathy and little or no concomitant vascular insufficiency or infection The lesion appears as a swelling of the midportion of the foot with or without pain and progresses to loss of both arches of the foot and finally to total disintegration of the tarsal bones and their articula tions Four cases are reported by Barkley Beidleman and Garfield G Duncan[4] (Philadelphia)

Two types of destructive lesions of the bones of the foot are demonstrable in such patients by roentgen examination (1) gradual dissolution of the tarsal bones and their artic ulations (the Charcot joint) attributable to diabetic neurop

(4) Am J Med 12 43 52, J[illegible] 1952

(Fig 111 10 13-48) A year later after he had withdrawn from school and was employed as a clerk re examination showed a normal curve (11 15 49) and he had no complaints He felt so well that the following spring he returned to school but soon had a recurrence of fatigue and an abnormally flat curve (5 12 50)

Psychotherapy designed to lessen the impact of external stimuli on dysadapted organisms (or to remove the stimuli) usually helps but regression is common It has also been possible to alter the end result of the stress syndrome by surgical vagotomy or by medical vagotomy with atropine Proper dietary management (high protein low carbohydrate diet) may also be of value both symptomatically and in altering the glucose tolerance curve Cortisone has been used in treatment of these patients but results are not predictable Sometimes the patient s symptoms are alleviated sometimes only the glucose tolerance curve is affected Further study of this and other therapeutic endeavors is needed for with the increase in noxious stimuli in the world problems of this nature will likely become more prevalent than before

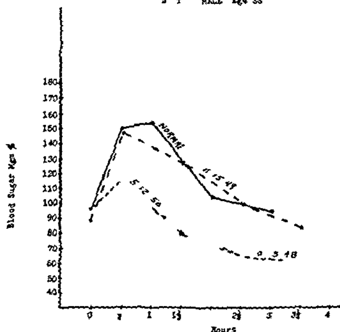
MINERAL METABOLISM

Etiology and Treatment of Serum Potassium Deficits are discussed by Helen Eastman Martin Telfer B Reynolds Edward N Snyder Clarence J Berne Ralph E Homann Jr Hugh A Edmondson Norman Blatherwick Irving Fields Maxine Wertman and Leola Westover[7] (Los Angeles) Intra and extracellular potassium deficits are caused by (1) inadequate intake resulting from restricted food intake or use of parenteral fluids which do not contain potassium and (2) accelerated loss of potassium from the body Accelerated excretion may be due to altered tubular function diuresis dehydration negative nitrogen balance from any cause or loss of gastrointestinal fluid through fistulas suction apparatus or diarrhea Extracellular potassium deficits occur with use of drugs which accelerate protein or carbohydrate synthesis in familial periodic paralysis or with any factor causing hemodilution

Symptoms of potassium deficit can usually be correlated with the serum concentration which also reflects intracellular

(7) J A M A 147 24 30 Sept 1 1951

ditions and pleasant or entertaining activities alleviate the fatigue As the condition continues even the pleasant activities fail to interest the patient Little evidence of structural change is found on examination Postprandial improvement is so common that carbohydrate metabolic studies have been done These show flat glucose tolerance curves (even when



F g 111 —Gl tole n e cu s (Cou t sy t C nk C A Jou al La t 71 484 487 No emb 1951)

individual blood sugar determinations are within normal limits) Three methods of treatment are possible (1) removal of stress stimuli (2) correction of the dysadaptation state and (3) correction of defective or inadequate hormone or neurogenic balance The first method is exemplified in the following case report

Man 33 was classed as psychoneurotic in military service because of fatigue and inability to concentrate These symptoms recurred in college being precipitated by a heavy academic load and an unhappy love affair A flat glucose tolerance curve was obtained

therapy Too much potassium was preferred to too little unless renal function was seriously impaired For correction of recent acute deficits 3 Gm potassium chloride intravenously in 24 hours is recommended in addition to the daily prophylactic dose For patients in diabetic coma 12 16 Gm potassium chloride should be given during the first 24 hours of intensive insulin treatment 2-4 Gm intravenously and 10 12 Gm orally In severe chronic deficits 10-20 Gm should be given intravenously or 10 Gm intravenously and 10 Gm orally if possible For infants 0 20 Gm /kg body weight daily is recommended

High serum potassium concentrations result from impaired glomerular filtration hemoconcentration rapid tissue breakdown or too rapid intravenous administration of potassium Therapy often difficult includes use of the artificial kidney induced diuresis by saline therapy shift of potassium to cells by use of insulin and dextrose and administration of calcium

[This article with many others illustrates the relatively frequent occurrence of abnormal blood potassium level Very low or very high levels are quite serious causing impairment of many important functions and death. Efforts at correction must be carefully conducted with repeated serum potassium determinations and ECG studies Such efforts are distinctly rewarding in this field —Ed]

Subperiosteal Resorption of Bone Roentgenologic Manifestation of Primary Hyperparathyroidism and Renal Osteodystrophy is discussed by David G Pugh[8] (Mayo Clinic) This bone change is seen most often along the margins of the phalanges of the hands especially the middle phalanges and gives a peculiar lacelike appearance to the bone beneath the periosteum Sometimes the external surface of the cortex has a ragged spicule like appearance resulting from bone resorption In extreme cases the cortex may be completely absorbed and when distal phalanges are affected the tufts tend to be absorbed At times subperiosteal resorption of bone occurs around the joint in which case the appearance suggests rheumatoid arthritis with no clinical evidence of the disease Other sites are along the medial aspect of the upper third of the tibia inferior aspect of the distal third of the clavicle and margins of the distal end of the ulna After the state of hyperparathyroidism has been corrected by operation subperiosteal bone is rapidly regenerated and the cortex

(8) Am J Roentgen 1 66 577 586 October 1951

levels if hydration and renal function are normal Symptoms and signs include weakness to paralysis of the muscles of trunk and extremities decreased motility of the gastrointestinal tract with adynamic ileus and cardiac muscle changes manifested by systolic murmurs gallop rhythm cardiac dilatation hypotension and ECG changes

The flame photometer was used in 6 190 serum potassium determinations on about 3 100 patients studied over two years The levels were high in 29 1% of determinations and low in

Basic Cause of Potassium Deficiency in 150 Cases*

	No Cases	Av No Days Cause Was Operative
1 Decreased intake of potassium		
A Poor food intake or none	41	16 3
B Nasogastric suction potassium free parenteral fluids previous poor food intake	90	5 3 of suction + 7 5 prev poor food intake
2 Increased potassium loss from gastrointestinal tract or *urine*		
A Diarrhea	4	11
B Ileostomy	1	14
C Desoxycorticosterone therapy	2	5
D Lower nephron nephrosis recovery phase	2	3+
3 Shift of potassium into cells		
Diabetic coma under insulin therapy	10	1
Total	150	

A id b b lan ly d sep t ly

6 2% The basic cause of potassium deficiency in 150 of the patients is given in the table

The problems in therapy were to find (1) the best solution and mode of administration (2) the prophylactic requirements for patients who did not eat and (3) the average amount of potassium required to correct acute and chronic deficits A stock solution containing 1 Gm potassium chloride in 15 cc distilled water was used the calculated amount of potassium thus being added to any intravenous solution required for other purposes Oral administration was not stressed since an adequate diet provides sufficient potassium for the patient able to eat Correction of deficits over several days was considered wiser than too rapid correction if symptoms were not alarming

On the basis of balance studies the average amount of potassium *chloride* for prophylaxis was found to be 3-6 Gm daily for patients requiring several days of parenteral fluid

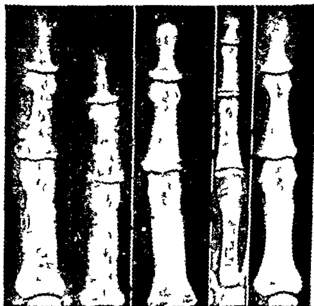
4 4 units In two patients cysts of the bone were seen without evidence of subperiosteal resorption this was explained in one by large amounts of milk consumed for duodenal ulcer and unexplained in the other An alkaline phosphatase concentration of only 5 3 Bodansky units in the latter patient indicates that for some reason the bone disease had become inactive In 25 patients subperiosteal bone resorption was evident and in 23 the level of alkaline phosphatase averaged 16 4 Bodansky units the highest value being 43 1 and the lowest 6 7 units

Of 35 patients with renal insufficiency 7 (6 children) had generalized decalcification with no rickets or evidence of subperiosteal resorption of bone 2 had rachitic changes without subperiosteal bone resorption and 26 showed subperiosteal bone resorption All seven without rickets had a low fixed specific gravity of the urine Serum calcium and serum phosphorus levels were normal in five patients on whom determinations were made Urea concentrations for seven averaged 105 mg /100 cc blood The creatinine level determined on the one adult was greatly elevated The two patients with rickets but no subperiosteal bone resorption had urea values of 118 and 74 mg /100 cc with a low specific gravity of urine for one Serum calcium levels were low and serum phosphorus levels normal Of the 26 with subperiosteal bone resorption all but 2 had definite acidosis The serum calcium level for 25 averaged 8 4 mg /100 cc and the serum phosphorus for 24 averaged 6 5 mg Eleven had an average of 22 7 Bodansky units for alkaline phosphatase Subperiosteal resorption of bone in the patients with renal osteodystrophy was identical with changes occurring in patients with primary hyperparathyroidism (Figs 114 and 115)

Subperiosteal resorption of bone does not occur in osteoporosis or hypervitaminosis D Evidence that it occurs only in primary hyperparathyroidism and in renal osteodystrophy seems ample There is also evidence to support the concept that in renal osteodystrophy with subperiosteal resorption of bone a state of secondary hyperparathyroidism is present and that it may be a direct effect of elevation of serum phosphorus on the parathyroid glands However in some patients the serum phosphorus content was not elevated so the mechanism is still obscure The type of parathyroid response

appears normal There is never any permanent loss of cortex and the tufts are completely re formed (Figs 112 and 113)

Study of 76 patients with primary hyperparathyroidism in whom parathyroid adenomas or primary hyperplasia of the parathyroid glands was demonstrated at operation showed that 38 had no roentgen evidence of disease of the bone



F g 112 (l ft) —Ren l st ody t phy n p t t g d 15 S bp t l p t of bo e phalanges de t l th that p ma y hype p athy od m.
F g 113 (t l ft) —R n l t ody t phy n p nt ag d 29 M t sp cu ous pt l g n d f m ddle phal
F g 114 (nt ght) —P ma y hype p thy d m bef em al of p a thy d d ma h w ng t n bp teal pt n of bo
F g 115 (ght) —3 b t y aft pe t S bpe ost al bone h be compl ly t l
(C t sy f P gh D G Am J R ntg n l 66 577 586 O tobe 1951)

33 of the 38 had urinary calculi Average alkaline phosphatase content of the serum in 33 patients was 2 9 Bodansky units with the highest value 6 units Three patients tested by the King Armstrong method had an average of 4 8 units In 11 patients slight or moderate decalcification of the skeleton was seen roentgenologically without evidence of subperios teal bone resorption The alkaline phosphatase level in 10 of the 11 averaged 3 4 Bodansky units the highest value being

the facial bone rarely show changes the face seems abnormally small in contrast to the calvarium

The bone arising from connective tissue in Paget s disease does not show the mosaic pattern Paget s disease manifests a natural tendency to spontaneous healing as evidenced by histologic examination Healing is associated with an attempt



Fg 116—f j j it l j a e f k ll d d I g t d e (C t y f G ld be g R R J Bo & J t S g 33 A 911 921 Octobe 1951)

to reconstruct more compact bone and as a result lamellar bone formation on a more normal basis appears on the walls of the enlarged vessel canals Vessel spaces become lined with osteoblasts and lymphoid marrow reappears in these spaces Roentgen examinations are of the greatest importance since they may reveal instances of osteoporosis circumscripta with involvement of the calvarium at an early age A frequent characteristic of Paget s disease is that though the outer table is porotic the inner table is sclerotic The roentgenologist must guard against confusing the rarefaction of osteoporosis

that occurs in renal insufficiency suggests that it may be truly toxic and not a purely compensatory mechanism

[It must be emphasized that (*a*) more than half the patients with proved *primary hyperparathyroidism have no roentgen evidence of bone* disease (*b*) renal disease is far more common and (*c*) rarely neither condition is demonstrable The bone changes of primary hyperparathy *roidism* and renal osteodystrophy may be quite similar However Pugh presents a good discussion of the differential diagnosis of these and other metabolic bone diseases —Ed]

Skull in Paget's Disease Raphael R Goldenberg[9] (Hosp for Joint Diseases New York City) studied six cases of osteoporosis circumscripta The affected skull area is a deep red violet and stands out sharply from the normal bone be cause the tables are thinned permitting the reddish color of the vascular marrow to shine through Vascular channels are increased in size and number and this increase is often as sociated with great vascularity which at times is severe enough to suggest venous thrombosis as the underlying pathologic condition The total thickness of the skull remains unchanged However such osseous tissue as is present in the area of osteoporosis circumscripta already presents the his tologic appearance of pagetic bone and the frontal area is the commonest site for the disease to appear As the area of osteoporosis circumscripta blends into the more typical lesions of Paget's disease the violet red color fades and eventually disappears yielding to the typical grayish or whitish appearance of the thickened skull As vascularity wanes a process of new bone formation begins in both tables this bone rapidly becomes diseased In advanced cases the cranium presents considerable alteration in structure principally in the calvarium in which involvement is often diffuse and the degree of thickening irregular and most pro nounced in the occipital region Skull circumference may increase considerably Knaggs stated that as vascularity de clines the cranial bones go through a stage of advancing sclerosis and the outer and inner surfaces become walled off by condensed bone of varying thickness The intervening portion shows various degrees of porous cavernous or can cellous tissue the spaces of which are filled with a soft reddish structure As new bone is being deposited one or more oval and patchy foci of sclerosis appear within the rarefaction Since

(9) J Bo & Jo t S g 33 A 911 921 Octobe 1951

coughing flushing nausea and occasionally vomiting The injection increases the serum iron from fasting level (SeFe) to total iron binding capacity of the serum (TIBC) represented by the five minute specimen The increase (INC) from SeFe to TIBC is the unsaturated iron binding capacity Decrease (DEC) in serum iron level from the 5 to the 120 minute specimen is apparently a function of the tissue uptake of serum iron

Seven hemochromatosis patients had 13 intravenous iron tolerance tests with the following characteristics (1) normal or high SeFe, (2) normal or low TIBC (3) high saturation of iron binding protein (4) normal DEC range and (5) high DEC/INC ratio Although average SeFe (213 μg/100 ml serum) exceeded normal (146 μg/100 ml) there was considerable overlap No SeFe value was below four were within and six of the other nine were well above normal range Normal fasting serum iron value does not therefore exclude the disease No TIBC value was above five were within and eight fell below normal range Since cirrhosis per se has similar TIBC values they alone are not diagnostically significant Degree of saturation of serum iron binding capacity exceeded normal in all seven patients although the highest individual normal (58%) approached lowest abnormal value (63%) Elevated serum saturation is evidently of great value in diagnosing hemochromatosis

Although absolute DEC in hemochromatosis fell within normal range DEC/INC ratio was always well above normal Three of the seven patients unlike any normal subject had decreased serum iron in the 120 minute specimen to a level below the fasting control figure and a resultant DEC/INC ratio exceeding 1 00 Abnormally high ratios in hemochromatosis indicate increased tissue affinity for serum iron under such conditions although strictly speaking they do not have this characteristic unless serum iron levels are artificially increased

Such abnormalities are not specific for hemochromatosis having been found in pernicious anemia in relapse Cooley s anemia acute leukemia and aplastic anemia The test is no less valuable in hemochromatosis as the other diseases are easily differentiated The major clinical difficulty is to differentiate simple portal cirrhosis from cirrhosis with hemo

circumscripta with the rarefied areas of bone destruction caused by tumors in the thickened and sclerotic calvarium of a pagetic skull

In Paget s disease serum calcium and phosphorus values are nearly always within normal limits whereas the phos phatase *value is usually elevated The elevated phosphatase* level noted in patients with osteoporosis circumscripta as sociated with Paget s disease is due to such foci of sclerosis *as may be present not to the osteoporosis circumscripta in* itself Review of literature fails to disclose a single instance of the disease diagnosed clinically Paucity of clinical symp toms serves to differentiate between the early and later stages of Paget s disease In the advanced stage (Fig 116) de formities of the spine femora and tibiae may cause consid erable weight loss and the enlarged head apparent lengthen ing of upper extremities waddling gait and bowlegs suggest a simian appearance Headache deafness and mental dis *turbances are frequent complications*

About 75% of all sarcomas develop in the age group 10 25 years A lesion evidently representing an osteogenic sarcoma developing in a person 50 or more should suggest *a complication of unrecognized Paget s disease* The sarcoma in Paget s disease is not necessarily osteogenic as a fibro sarcoma may develop instead with more favorable prognosis Usual life expectancy after development of sarcoma is about one year

[The cause of this disease is unknown but it is not endocrine The disease occurs not uncommonly in the aged It may involve from 1 to 95% of the bones but some normal bone is always present Osteogenic sarcoma is a common complication There is no satisfactory treatment —Ed]

Metabolism of Iron I Intravenous Iron Tolerance Tests in Normal Subjects and Patients with Hemochromatosis Stanley E Gitlow and Milton R Beyers[1] (V A Hosp Bronx N Y) tested fasting subjects by slow intravenous administra tion of saline diluted green ferric ammonium citrate equivalent to 10 mg elemental iron Serum iron was measured in speci mens drawn before and 5 and 120 minutes after injection The quantity of iron exceeds that needed for complete satura tion of the serum *iron binding protein* The excess *rapidly* diffuses into tissues causing such toxic symptoms as sneezing

(1) J Lab & Cl M d 39 337 346 Ma h 1952

manifestations were controlled (7 36 days) Daily amounts of cortisone were then gradually decreased in a steplike manner every four to seven days—by 10 mg a dose for intramuscular administration and by 12 5 mg (one half tablet) for oral medication The smallest daily amount which would adequately control clinical manifestations was considered the patient s maintenance dose Attempts were not made to restrain the disease completely unless this could be accomplished with relatively small doses as in some less severe cases The maintenance dose was not fixed throughout the course of treatment but was usually manipulated from time to time Ability to maintain satisfactory improvement varied indirectly in general with the severity of the disease Very marked or marked antirheumatic response was upheld for long periods in 47% of severe 70% of moderately severe and 92% of moderate and mild cases The chief obstacle to better results in the severer cases was appearance of adverse hormonal effects which developed frequently when relatively large maintenance doses were required to support satisfactory improvement Most of them were mild or transient and disappeared or lessened when the dose was reduced

At first moderate to marked gains in weight occurred routinely but when caloric intake was curtailed as soon as the optimal body weight was reached excessive gains were avoided Increased deposit of fat in the cheeks was manifested by 12 patients 9 of whom were receiving relatively large daily doses (75 mg or more) This condition usually improved or was corrected by decreasing the dose Two instances of so called buffalo hump due to fat deposit in the back of the neck were noted

Decreases in carbohydrate tolerance developed in three patients—one with a normal pretreatment curve and two with latent diabetes mellitus beforehand Glycosuria was well controlled in each instance with moderate dietary restriction of carbohydrates (and without insulin) and there was no tendency toward progressive impairment of carbohydrate metabolism Edema developed in nine women seven of whom were receiving 75 mg or more of the hormone each day Invariably it responded readily to reduction in dosage and dietary restriction of sodium and diuresis could be hastened by giving saline or mercurial diuretics Later edema and

chromatosis For this the iron tolerance test is definitely helpful Compared with hemochromatosis such tests in cirrhosis have revealed (1) slightly lower SeFe (2) lower saturation (3) similar TIBC ranges and (4) lower DEC/INC ratio Tendency toward low TIBC values in both diseases might be due to altered protein metabolism in chronic liver disease with specific difficulty in forming iron binding protein

[Repeated phlebotomies are associated with increased liver function and erythrogenesis and decreased quantities of free iron—the toxic agent in hemochromatosis —Ed.]

RHEUMATOID ARTHRITIS AND GOUT

Despite many advances the treatment of these disorders leaves much to be desired It is apparent that the adrenal corticoids are only palliative not curative Rheumatoid arthritis often relapses following cessation of cortisone yet continuous therapy in doses sufficient to cause desired relief is associated with undesirable effects from the drug in over a third of the patients Thus a regimen of suboptimal doses is administered for an indefinitely prolonged interval Hydrocortisone apparently has a more potent antirheumatic effect with fewer of the undesirable effects Pregnenolone desoxycorticosterone and indeed all other steroids have not proved very atisfactory

It is evident that this type of steroid therapy for rheumatoid arthritis must be accompanied by appropriate psychotherapy physiotherapy mental and physical relaxation and in many instances chrysotherapy —Ed

Prolonged Uninterrupted Cortisone Therapy in Rheumatoid Arthritis Edward W Boland[2] (Los Angeles) reports observations on 45 women and 31 men aged 19 80 who were given cortisone in the hope that treatment could be continued uninterruptedly for extended periods No other medications which would influence the course of the disease or provide symptomatic relief were permitted and analgesics physical therapy and other supportive adjuncts were stopped For various clinical reasons it was necessary to discontinue treatment in 16 patients within the first six months but the other 60 received the hormone uninterruptedly for 6-15 months Oral preparations were given to 54

Patients with severe or moderately severe arthritis were given 200 or 300 mg cortisone for one or two days followed thereafter by 100 mg daily those with moderate or mild cases were given 100 mg on the first and subsequent days These suppressive amounts were continued until clinical

(2) B it M J 2 191 199 J ly 8 1951

sone acetate given orally However response to free compound F was more uniformly rapid and even with smaller suppressive doses clinical improvement was faster and elevated sedimentation rates were corrected sooner than with cortisone acetate Usual initial dosages with cortisone acetate have been in severe and moderately severe cases 200 or 150 mg daily for the first one or two days with 100 mg daily thereafter for moderate and mild cases 100 mg on the first and subsequent days Using free compound F three patients with moderately severe and one with moderate rheumatoid arthritis were given 100 mg the first day and for several days thereafter A patient with severe disease took 150 mg daily for 2 days and 100 mg/day for another 13

By transferring 10 patients already stabilized on maintenance doses of oral cortisone acetate to free compound F dosage requirements for similar degrees of clinical improvement were compared Free compound F was consistently more potent than cortisone acetate in antirheumatic activity Maintenance dose of cortisone acetate was 62 5 mg daily in 5 of the 10 patients Dosage ratios of cortisone acetate to free compound F ranged from 1 43 1 to 1 7 1 average ratio for the group was 1 56 1 thus potency of free compound F was roughly 50% greater The greater antirheumatic activity of free compound F did not involve a correspondingly greater tendency to adverse hormonal effects Several patients with endocrine complications while taking larger doses of cortisone acetate lost them entirely or partly when given smaller but equally effective doses of free compound F

Results with compound F acetate varied widely and dosage differences were not as clearly defined as with other preparations Generally it was less effective than either free compound F or cortisone acetate Compared with free compound F much larger suppressive doses were required for similar initial response and much greater maintenance doses were needed eight test patients needed nearly twice as much compound F acetate for equivalent rheumatic control Lower solubility of compound F acetate could substantially lower rate and degree of alimentary absorption and partly accounts for its therapeutic inferiority when given orally Free cortisone and cortisone acetate appeared equally effective in suppressing inflammatory rheumatic manifestations

sudden weight gains were largely avoided by placing patients on salt poor diets at the beginning of treatment while initial suppressive doses were given and by continuing this restriction if maintenance doses greater than 50 mg daily were used Potassium depletion was not observed Oligomenorrhea was encountered in three patients two of whom had other signs of increased androgen activity (hypertrichosis in one and acneiform eruption in the other) Spontaneous fractures developed in two patients (aged 65 and 66) The degree of mental stimulation seemed to depend mainly on the size of the dose administered Insomnia and restlessness for example,

RESULTS OF CORTISONE THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED CONTINUOUSLY FOR 6 15 MONTHS

SEVERITY OF DISEASE	NO OF CASES	AV MAINTENANCE DOSE MG	IMPROVEMENT MAINTAINED			ADVERSE EFFECTS
			Very Marked	Marked	Mod	
Severe	25	80 5	1	16	7	14
Moderately severe	23	64 1	8	11	4	8
Moderate	11	55 4	8	3	0	2
Mild	1	37 5	1	0	0	0
Total	60	68 8	18	30	11	4

Very marked and marked improvement was considered adequate and moderate and slight inadequate Only one with severe involvement had slight improvement.

were rarely troublesome with daily doses of 75 mg or less A pronounced degree of mental stimulation occurred transiently in two patients but no real mental depression or maniacal behavior was encountered

During prolonged cortisone therapy evidence of functional suppression of the adrenal cortices as indicated by a decreased response of circulating eosinophils to exogenous ACTH was present Depression of cortical function was temporary however and in patients from whom cortisone was withdrawn after 6 14 months of continuous therapy tests of adrenocortical function returned to normal in 10 90 days The general results of treatment are given in the table

Compound F Used Orally in Patients with Rheumatoid Arthritis Edward W Boland and Nathan E Headley[3] (Los Angeles) gave free compound F (17 hydroxycorticosterone) orally to 15 patients with chronic rheumatoid arthritis The hormone suppressed disease activity most effectively and with short term administration maintained control of rheumatic manifestations The pattern of improvement with initial suppressive doses generally resembled that noted after corti

3 J A M A 148 981 987 M 2 1952

before gold levels would be high enough to be effective and (3) cortisone may be discontinued in patients who respond to gold

Late Results of Gold Treatment in Rheumatoid Arthritis N Egelius N G Havermark and G Nystrom[5] (Stockholm) re examined 210 rheumatoid arthritis patients (two thirds were female) 5 15 years after gold treatment eliminating anyone who had received less than 0 8 Gm gold The patients were classified as asymptomatic improved unchanged or deteriorated No correlation was found between initial improvement and long term prognosis Prognosis was distinctly more favorable in males 28% of whom were symptom free 31% improved 15% unchanged and 26% deteriorated Among female patients only 9% were symptom free 30% improved 17% unchanged and 44% deteriorated The symptom free group comprised 15% of the entire series a figure well in keeping with the 10 15% of other investigators another 30% had improved The two groups together represented 45% of the total 38% had deteriorated

It appears important to begin gold therapy early Patients who began gold treatment a year after onset of the disease had far better results than those who began it later Of patients treated with gold within a year of onset 56% were symptom free 37% improved 44% unchanged and 26% deteriorated Corresponding figures for those treated with gold after the lapse of one year showed no such preponderance of the symptom free improved and changed conditions were fewer and deteriorations more frequent A shorter interval between first and second gold treatments was recorded for the more successful cases

Patients with disease starting at an early age had better prognoses than those who acquired it later Of the asymptomatic group 41% had fallen ill before age 30 Corresponding incidence for those improved unchanged and deteriorated was 27 26 5 and 14%

Clinical and Metabolic Effects of Benemid in Patients with Gout John H Talbott Charles Bishop Bernard M Norcross and L Maxwell Lockie[6] (Univ of Buffalo) tested benemid in more than 30 patients with typical acute or chronic

(5) Ann. Rheumat. D 11 17 22 Ma h 1952
(6) T A Am. Phys ci 64 372 377 1951

[Other investigators have also found hydrocortisone superior to its acetate and to cortisone and its acetate in rapidity of action and potency of antirheumatic effect. Cortisone is associated with more of the Cushing's disease type of complications. Hydrocortisone is reported to be distinctly more effective than cortisone when administered directly into an inflamed joint.—Ed.]

Cortisone and Gold Therapy in Chronic Rheumatoid Arthritis. Harry E. Thompson and Harold J. Rowe[4] (Tucson) studied the combined therapy in 8 patients who responded only partially to gold therapy and for whom cortisone was added to gold. 13 others took gold and cortisone concurrently. Of the 13, 7 had received gold before the investigation and therefore may not have been as responsive to gold. Cortisone was given intramuscularly in 100 mg. doses every 8 hours for 24 hours, then every 12 hours for 24 hours, then once daily for 21 days. It was then discontinued until relapse when it was reinstituted at the previous level; after 14 days 75-100 mg. was given parenterally every other day or 50-75 mg./day orally. It was again discontinued after varying intervals. A dose of 10 mg. gold was first given intramuscularly or intravenously; after that 50 mg. was given at weekly intervals until total dosage reached 1.0 Gm. Gold was then continued at 10, 14, 21 and 30 day intervals.

Results indicate that gold given with moderate benefit to patients with active chronic rheumatoid arthritis did not accrue the capacity to arrest the disease when cortisone was added. Despite excellent therapeutic response, remission was never complete; all patients relapsed to precortisone state soon after the hormone was discontinued.

Gold given concurrently with cortisone seemed to arrest rheumatoid arthritis about as often as gold alone but seemed superior to cortisone alone and to therapy without gold or cortisone. Concurrent administration produced excellent results with immediate increase in functional capacity and in some patients complete remission of arthritis. The effects were lasting often enough when cortisone was discontinued to be of therapeutic significance. Concurrent administration of gold and cortisone also has several therapeutic advantages: (1) patients previously intolerant to gold can take it in combination with cortisone with less danger of reaction; (2) cortisone permits immediate institution of rehabilitative measures long

(4) Ann. Int. Med. 36: 992-1000, Ap. 1, 1952.

instrument After observations on the eating behavior of the animals histologic preparations of the hypothalamus were made to confirm site of destruction In the most lateral part of the lateral hypothalamus there is an area apparently essential to eating Unilateral lesions have no effect but bilateral destruction leads to complete cessation of eating Conversely lesions in the ventromedial hypothalamic nuclei (or between these nuclei and the lateral ones) produce hyperphagia and obesity (Fig 117) In obese animals subsequent destruction of the lateral areas again causes cessation of feeding

Lateral hypothalamic areas have also been stimulated by

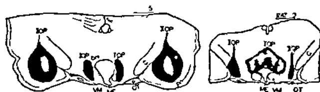


Fig 117—M d l l p od d t fi at per t n (I Op) l d to hype phagia d be ty At ec d ope t l on of mygd l w mad f th t dy (C t y f A d B K d B obe k, J R Yal J B ol & Med. 24 123 140 No ember 1951)

implanted electrodes in unanesthetized cats such stimulation causes a pronounced increase in food intake which returns to normal when stimulation ceases The lateral hypothalamic areas involved may be considered a feeding center as it appears responsible for the central hunger reaction or urge to eat The ventromedial center may influence the lateral feeding center by inhibitory fibers

[An important observation showing the enormous effect of small areas in the hypothalamus on food consumption Injury of one area causes pronounced obesity whereas injury of a nearby area produces decided malnutrition —Ed.]

Accumulation of Serum Cholate and Its Relationship to Hypercholesteremia. Meyer Friedman Sanford O Byers and Ray H Rosenman[8] (Mount Zion Hosp San Francisco) have obtained evidence which indicates that cholate accumulates in rats when cholesterol does Moreover cholesterol rise appears to be secondary to hypercholatemia Analyses were therefore made of the serum cholesterol and cholate values in

(8) S 115 313 315 Ma 21 1952

tophaceous gouty arthritis and in several nongouty controls Concentration of serum uric acid decreased after benemid ingestion in each instance and when measured urinary uric acid increased The effect of benemid on uric acid metabolism may be apparent within six hours of ingestion and with doses employed (1 2 Gm /day) the effect was maximal in 48 72 hours After benemid is taken for weeks or months its effect on serum uric acid may diminish but even after prolonged intake it was never ineffective as a uricosuric agent No toxic effects of clinical significance were noted Patients continued to have periodic acute attacks of gout but they were not interpreted as toxic reactions

Man after intermittent attacks of acute gouty arthritis for over 15 years wa given 0 5 Gm benemid four times daily Never before benemid therapy had his serum uric acid level been below 10 mg /100 ml after one week on the drug it was 4 mg /100 ml Benemid wa continued and 10 days later minimum concentration of 2 1 mg was recorded In the next eight months with benemid daily serum uric acid concentration ranged from 2 3 to 4 6 mg /100 ml During the first three months he had two attacks of acute gout This corresponded to frequency of attacks for a control period of similar length Subsequently he went five months with no acute attack. This was a longer period than usual

Benemid presumably inhibits the transport of uric acid in the kidney from the glomerular filtrate into the blood stream Uric acid is believed to appear in glomular filtrate in the same concentration as in a protein free filtrate of serum About 10% of filtered uric acid is excreted in bladder urine the rest is reabsorbed by the renal tubules Benemid increases the quantity filtered for excretion to as much as 15% As to total quantity every 24 hours 30 50% more urinary uric acid is excreted after therapy

[Other studies have also offered promise for the use of benemid as adjunctive therapy to colchicine in gout —Ed]

MISCELLANEOUS METABOLIC DISORDERS

Hypothalamic Control of Food Intake in Rats and Cats is demonstrable according to Bal K Anand and John R Brobeck[7] (Yale Univ) by making minute lesions in this structure Electric currents were used to destroy regions reached by fine needles inserted by means of a stereotaxic

(7) Yale J Biol & Med 24 1 3 140 November 1951

to porphyrin It does not give a positive reaction with Ehrlich s reagent

The porphyrin cont nt of bone marrow was essentially normal in the intermittent acute and mixed types However the liver contained significant increases In the intermittent acute type this was chiefly found as a precursor which is converted to porphyrin on heating Native porphyrin was found in the liver in a case of mixed type In cases of photo sensitivity the bone marrow contained large amounts of porphyrin chiefly in the developing normoblasts (predominantly as uroporphyrin I)

The authors propose a fundamental classification of porphyria (1) porphyria erythropoietica—photosensitive or congenital type often associated with hemolytic anemia and splenomegaly and sometimes benefited by splenectomy (2) porphyria hepatica subdivided into (*a*) intermittent acute porphyria with abdominal or nervous manifestations and (*b*) mixed porphyria with late appearance of photosensitivity and episodes of abdominal and/or nervous symptoms

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THYROID GLAND

Identification of 3 5 3 1 Triiodothyronine in Human Plasma has been accomplished by J Gross and Rosalind Pitt Rivers[1] (Nat l Inst for Med Research London) Samples of plasma were taken from hyperthyroid and euthyroid patients and butanol extracts made Doses of radioiodine varying from 100 μc to 100 mc were given at different times before the plasma was taken Two dimensional paper chromatograms were made of the plasma extracts and the resultant auto radiograms compared with those obtained using synthetic triiodothyronine and thyroxine Radioactivity counts were made on partitions of modified kieselguhr column By adding synthetic radioactive thyroxin to plasma it could be shown that the activity corresponding to triiodothyronine was not a result of extraction procedures As the iodine containing substance in plasma of patients given radioactive iodine behaves identically with that of 3 5 3 1 triiodothyronine it is

(1) I t 1 439 441 Ma 1 1952

25 normal patients 12 with nephrosis 6 with xanthoma 5 with diabetes 8 with myocardial infarct and 2 with hypothyroidism The normal subjects had average serum cholate of 5 3 mg /100 ml and average serum cholesterol of 228 mg /100 ml Hyper cholesteremia was invariably associated with elevation of serum cholate Whereas cholesterol/cholate ratio in normal subjects was 43 it ranged only from 29 to 33 in diseased sub jects

Experimental accumulation of cholate is followed by hyper cholesteremia Biliary obstruction and experimental nephrosis lead to hypercholatemia which in turn is followed by hyper cholesteremia These observations suggest that clinical hyper cholesteremia may be a phenomenon secondary to initial derangement of cholate metabolism This implies importance of the liver when evaluating factors involved in the patho genesis of hypercholesteremia in man

[These and other of Friedman s studies show that the blood cholate content is increased in most patients with hypercholesteremia How sig nificant hypercholatemia is in atherosclerosis has not yet been properly evaluated —Ed]

Manifestations of Different Forms of Porphyria in Rela tion to Chemical Findings C J Watson P T Lowry R Schmid V E Hawkinson and S Schwartz[9] (Univ of Minne sota Hosp) report data an 88 cases of porphyria divided as follows intermittent acute type 60 latent (no attacks or symptoms) 13 mixed (cutanea tarda or chronic) 10 and congenital photosensitivity 5 In the intermittent acute type there were episodes of abdominal and/or neurologic mani festations Ehrlich reacting porphobilinogen was present in the urine during these attacks but disappeared during re missions The aldehyde compound is chloroform insoluble in contrast to urobilinogen Porphobilinogen was absent from the urine in the congenital photosensitive and also in the mixed cases in which only photosensitivity was present but in several mixed cases it was evident with onset of abdominal pain or nervous or psychic abnormalities

Porphobilinogen when isolated yields dark brown porpho bilin on heating in acid solution It can be separated from another compound found in the urine in porphyria this chromogen is a uroporphyrin precursor and can be converted

(9) Tr A Am. Phy a 64 345 352 1951

pound U from labeled thyroxin homogenized liver is not kidney slices showed some activity but heart diaphragm spleen and brain were inactive in this reaction

Thyroid Thyrotrophic Hormone Balance in Blood of Normal and Endocrinopathic Individuals is reported by Savino A D'Angelo Karl E Paschkis Albert S Gordon and Abraham Cantarow[3] Change in thyroid cell height of developmentally static tadpoles is found to be a sensitive bioassay for thyroid stimulating hormone (TSH) Relative serum TSH thyroid hormone balance evaluation is possible by comparing serum induced growth of the hindlimbs with that after injection of known amounts of pure TSH

Serums from normal persons showed low TSH activity with relatively high thyroid hormone content Three persons with acromegaly showed an average eightfold increase over normal TSH but had normal thyroid activity In three patients with Simmonds disease no TSH or thyroid activity was found In those with hyperthyroidism normal TSH titers were found in serums having high amounts of thyroid thyroid hormone was consistently low but TSH ranged from none to high Treatment with thyroid resulted in clinical improvement without restoration of normal TSH thyroid balance Serum from exophthalmic patients gave results similar to normal serum except in two whose TSH levels were high These findings do not show reciprocal regulation of the pituitary thyroid axis thought to occur in variations from the euthyroid state

Somnolent Metabolic Rate (SMR) as Aid in Differential Diagnosis of Thyroid Dysfunction Richard L Rapport George M Curtis and Sarah Jane Simcox[4] (Ohio State Univ) describe a method of determining the metabolic rate under intravenous nembutal® anesthesia and term this the somnolent metabolic rate Light anesthesia is induced by 100-300 mg nembutal® and metabolic rate taken in the usual manner

A total of 200 evaluations of the rate was made in 152 patients with varying degrees of normal elevated or depressed thyroid function There was excellent correlation with both clinical diagnoses and serum protein bound iodine

(3) J Cl E doc J 11 1237 1253 N mbe 1951
(4) Ib d. pp 1549 1563 Decembe 1951

concluded that this material is a normal constituent of the organic iodine fraction of plasma It is found in plasmas of both euthyroid and hyperthyroid individuals

[In another study (Lancet Mar 22 1952) these workers reported that triiodothyronine is about three times as active as l thyroxin in preventing thiouracil goitrogenesis in rats

These observations and the ones described in the next two articles dealing with the metabolism of the thyroid hormone may contribute greatly to understanding of the role of this hormone in general body metabolism —Ed]

I^{131}-Labeled L Thyroxin II Nature of Excretion Product in Bile When bile was collected from adult rats into which radio L thyroxin had been injected subcutaneously it was found that much of the I^{131} was in the form of an unidentified compound which corresponded to no known iodine compound of mammalian tissue Alvin Taurog F N Briggs and I L Chaikoff[2] (Univ of California) isolated the compound (compound U) from filter paper chromatograms Location of compound U was determined from the corresponding radio autograph Hydrolysis with barium hydroxide solution released thyroxin from compound U along with some diiodothyronine and inorganic iodine

Urine of rats given injections of radiothyroxin contained chiefly inorganic iodine Feces from such animals were collected and extracted Chromatography revealed no compound U in the feces With the bile excreted into the gastrointestinal tract and with total iodine content of the feces about the same as that of the bile it appears clear that compound U is hydrolyzed as it passes through the intestinal tract liberating thyroxin which can be identified in the feces Inorganic iodine also appears in the feces

In vitro attempts to hydrolyze compound U by trypsin chymotrypsin carboxypeptidase pancreatic extract and extract of intestinal mucosa were uniformly unsuccessful Contents of the lower small intestine or large intestine of the rat were capable of hydrolyzing compound U Beta glucuronidase was also capable of splitting compound U with release of thyroxin It is possible but not certain that thyroxin is coupled with a glucuronoside structure to form compound U a peptide structure can be ruled out by failure of other enzymes to hydrolyze compound U

Surviving rat liver slices are capable of forming com

(2) J B l Chem. 194 655 668 F bruary 1952

Minnesota) studied and standardized the procedure so that apparently 0 1 μg iodine added to normal serum could be completely recovered Standards for serum protein bound iodine (PBI) were drawn from 402 young and middle aged white men diagnosed as euthyroid and followed for three years Frequency distribution of serum PBI values is significantly peaked and skewed so that standard deviations are inappropriate measures of dispersion (Fig 118) No significant correlation was observed between age and serum PBI but

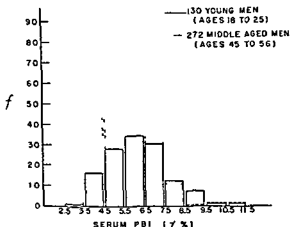


Fig 118—F q y d t b t f rum PBI l mal m (Courtesy f T k R G d K y A J Cl n I t 30 869 873 A gu t 1951)

normal middle aged men (45 56) have significantly lower serum PBI than normal young men (18-25) A slight but significant positive correlation was found between serum PBI and the basal metabolic rates Middle aged men but not the younger men showed a positive and linear correlation between serum PBI and serum cholesterol concentration No relationship between serum PBI and relative obesity of the individual could be found in any of the men Mean value for serum PBI in young men was 6 24 middle aged men 5 63 and for the combined group 5 83 μg/100 ml

[The PBI test should be used much more frequently There are many commercial laboratories that run th s test it is ava lable to all phys cians —Ed]

values Of the rates 91% were compatible with the clinical diagnosis whereas only 67% of average basal metabolic rates taken previously and 62% of those determined immediately before nembutal® anesthesia showed compatibility Average fall of the metabolic rate in hypothyroid and euthyroid patients with a clinical diagnosis of underlying nervous states was 32% whereas average fall in other patients in these two groups was only 8 5% In hyperthyroid patients it was difficult clinically to separate extrathyroidal hypermetabolism from true hyperthyroidism Average fall in all patients in this group was 13% as compared to 14% in hypothyroid patients and 15% in euthyroid patients

Intravenous administration of nembutal® requires neither hospitalization nor assistance of a trained anesthetist The results of single evaluations of the basal metabolic rate are unreliable and those of serial evaluations may be erratic whereas initial single determinations of the somnolent metabolic rate give significant information concerning thyroid function In hypothyroid patients with a normal or elevated BMR the SMR will often reveal the true diagnosis In euthyroid patients with an elevated BMR the SMR will reveal elevation as a result of extrathyroidal hypermetabolism rather than of true hyperthyroidism Although the serum protein bound iodine test is generally accepted as more reliable than the BMR as an indicator of functional thyroid disorders the former may be affected by exogenous iodine in any form and is of no value in iodinated patients Radioactive iodine tracer studies may also be affected by exogenous iodine

Both protein bound iodine and I^{131} uptake values depend on the functional activity of the thyroid whereas the SMR is an index of the total effect of thyroid hormone on end organs All three studies should be done in patients with thyroid dysfunction

[Strong sedation is of distinct advantage in some patients particularly in those with anxiety neurosis However I prefer not to use intravenous medication unless oral is unsatisfactory If intravenous therapy is required it is safer to hospitalize the patient —Ed]

Concentration of Serum Protein Bound Iodine in Normal Men is determined by a colorimetric technic which can be made most reliable Robert G Tucker and Ancel Keys (Univ of

(5) J Cl I t 30 869 873 A gu t 1951

mg daily controlled about 87% and 300 mg 96% About 4% required over 300 mg daily The drug must be given in at least four daily doses because each dose is effective only a few hours Signs of toxicity are fever arthralgia *leukopenia and skin eruptions It may be necessary to dis* continue treatment in 2 5% of patients owing to toxic symp toms and occasionally to thyroid enlargement Frequent white blood cell counts are unnecessary but if symptoms of agranu locytosis (sore throat or fever) appear the drug is dis continued and penicillin and blood transfusions are given Patients are observed at one to two month intervals Maximal rate of response is a daily fall of about 1% in basal metabolic rate To avoid the excessive vascularity of the gland which may accompany the use of the thioureas 10 20 mg iodine is given daily during treatment Desiccated thyroid is also used if the BMR falls below —10% *The same dose of thiouracil may* be continued unless thyroid enlargement necessitates reduction *to the minimal dose required for regulation Treatment is* continued 9 12 months after symptoms are controlled and a normal BMR has been established thereafter if symptoms and metabolic rate permit 65 130 mg desiccated thyroid may be given daily in the hope that it will suppress the pituitary enough to reduce the recurrence rate

In 18 patients hyperthyroidism was not controlled In some larger doses might have been effective Failure in the others is attributed to poor patient co-operation or discon tinuation of the drug because of toxicity Seventy patients were in remission when last heard from Of these 89% main tained a *remission for at least six months after stopping* treatment Conversely 78% of relapses occurred before the *sixth month* Results of *thiouracil treatment are related to the* type of goiter remissions being maintained in 66% of pa tients with previously untreated Graves disease and in only one third of those with nodular goiter and postoperative re currences In 60 patients with Graves disease considered most suitable for this treatment remission rate was 77% These drugs are definitely useful in hyperthyroidism both pre operatively and to control patients not suitable for surgery and for a definitive cure of Graves disease

Radioactive iodine was given to 360 patients principally with Graves disease The initial dose is based on gland size

Hyperthyroidism without Apparent Hypermetabolism occurs as a poorly recognized entity but with the aid of radioiodine uptake and serum percipitable iodine (SPI) studies Sidney C Werner and Howard Hamilton[6] (Columbia Univ) were able to diagnose 15 such cases in one year The patients were aged 21 61 and included 13 women In each case there was a clinical suspicion of hyperthyroidism Frequent symptoms were nervousness weight loss with good appetite palpitation and fatigability All patients had pulse rates between 86 and 120/minute Moist warm palms a palpable thyroid and fine tremors were less constant BMR ranged from + 1 to + 16% Radioiodine tracer uptake varied from 38 to 77% with nine values over 50% SPI levels ranged from 8 4 to 25 9 μg /100 cc Fasting serum cholesterol levels followed no definite trend

Treatment with radioiodine (six patients) propylthiouracil (five) sodium iodide (two) and surgery (one) caused a definite fall in BMR return of SPI levels toward normal and slight rise in serum cholesterol in all Since the correlation between tracer uptake and hormone release may be disrupted by therapy this was not restudied One patient was lost to follow up No response to therapy was obtained in two additional patients with laboratory data consistent with a diagnosis of hyperthyroidism Thus rigid criteria for diagnosis of hyperthyroidism must be maintained and must include a favorable response to therapy In doubtful cases information can be gained from a two week therapeutic test with potassium iodide A positive response includes a return of toxicity on cessation of therapy as well as a decrease thereof while the drug is being given

[I too have seen everal of these patients but I want to re emphasize the authors caution about making the diagnosis with insufficient evidence Normal BMR s vary a great deal Should the normal BMR of a patient be minus 20 he could have an elevation of 30 points and still be within the usual normal range—Ed]

Results of Nonsurgical Treatment of Hyperthyroidism are discussed by E Perry McCullagh[7] Opinions regarding propyl and methylthiouracil are based on a study of 179 patients with previously untreated or recurrent Graves disease or nodular goiter Dosage of 150 mg propylthiouracil daily controlled about 58% of patients within 2 months 200

(6) J A M A 146 450 453 J 2 1951
(7) Clevel d Cl Q art. 18 102 116 Ap il 1951

permitted continuation of therapy None of the patients had granulocytopenia but one instance was seen after this series of 100 patients was expanded Apparently larger doses are more apt to produce skin reactions Myxedema occurred in two patients but in none with hyperthyroidism due to adenomatous goiter Serial determinations of blood cholesterol values are therefore used as a guide to antithyroid treatment

Patients with primary hyperthyroidism were given Lugol s solution in addition to tapazole for three weeks before operation when these glands were found to be satisfactorily involuted Patients with adenomatous goiter were not given Lugol s solution

[The results reported are similar to those observed by several other investigators Apparently several thousand patients must be studied before it can be determined definitely whether tapazole is less toxic than propylthiouracil The former has an antithyroid effect in patients that is about 10 times as great as that of propylthiouracil —Ed.]

Therapeutic Studies in Hyperthyroidism Sodium 5 Iodo 2 Thiouracil Boris Catz Donald W Petit and Paul Starr[9] (Univ of Southern California) used iodothiouracil in doses of 50 800 mg daily in treatment of 26 unselected patients with thyrotoxicosis In 21 it was used in preparation for surgery in 3 as an adjunct to radioiodine therapy and in 2 provided long term medical therapy Potency was evaluated by determining (1) the degree of antithyroid action as measured by maximal clinical response blocking of radioiodine uptake and thyroid iodine content and (2) the degree of goitrogenic action measured by changes in thyroid size clinical observation and histologic change in the mean acinar cell height

Maximal clinical response occurred within 8 days in 10 patients 16 days in 7 and 22 days in 5 In four patients the response was slower or incomplete Optimal dose was 200 400 mg daily larger doses did not improve clinical response

In four patients tested there was inhibition of uptake of radioiodine In nine surgical specimens analyzed both total iodine and protein bound iodine contents were reduced below average values for normal tissue although serum protein bound iodine is increased in patients treated with the drug In all patients the thyroid remained the same size or decreased acquiring a characteristic firmness or tendency

(9) J Cl E docn 1 11 978 995 S pt mbe 1951

and severity of hyperthyroidism If essential for temporary control iodine or propylthiouracil may be given after treatment Response is evaluated in two months and if the BMR has not fallen the whole dose is repeated If the rate has fallen to about 30% half the original dose is repeated If it has fallen to around 20% and symptoms continue to improve no further treatment is given because hypothyroidism may occur as late as four months after the original dose The average curative dose approximates 10 mc but as much as 80 mc is sometimes needed Results are excellent No complications have arisen except hypothyroidism which occurred in 10% of patients and this may be transitory Radioactive *iodine is the least suitable major treatment for hyperthyroidism* of nodular goiter the required dose being much larger than that needed in Graves disease (average 34 mc) and the response slower It may be used in these cases however when surgery is contraindicated

[The 50% incidence of sustained remissions following antithyroid therapy in a series of unselected patients with thyrotoxicosis is in accord with my experience as well as that of Asper and Wing (Bull Johns Hopkins Hosp 90 201 1952) I believe that physicians should treat a greater proportion of patients with antithyroid drugs If one or two courses of about nine months each fail the patient can still be treated satisfactorily with surgery or radioiodine —Ed.]

1 Methyl 2 Mercaptoimidazole New Active Antithyroid Agent, is known as tapazole Elmer C Bartels and Robert W Sjogren[8] (Lahey Clinic) have used the drug in 100 patients 82 *of them with primary hyperthyroidism and* 18 with hyperthyroidism due to adenomatous goiter Age span was 10 75 years with 85% female patients Drug dosage was increased above that originally suggested so that the recommended dose is now 20 30 mg daily for patients with primary hyperthyroidism and 30-40 mg for those with adenomatous goiter (depending on size of goiter) Tapazole thus appears to be about 10 times as active as propylthiouracil Most patients were treated 40 70 days (93 of them received the drug in preparation for thyroidectomy) Seven patients were being *maintained in euthyroid condition after* 10-17 months with 2 5 5 mg tapazole daily

Six patients (6%) had skin reactions in three they were severe enough to warrant discontinuance of treatment In the others dose reduction and administration of antihistamines

(8) J Clin Endocrinol 11 1057 1062 October 1951

area for area basis The directional counter is used for outlining or mapping the thyroid gland in thyrotoxicosis With this instrument one can determine the completeness of thyroidectomy and locate accessory thyroid areas adenomas and metastases

For outlining a gland in hyperthyroidism 75 100 μc carrier free I^{131} in saline solution is given intravenously to the patient 48-72 hours before mapping A manual scanner

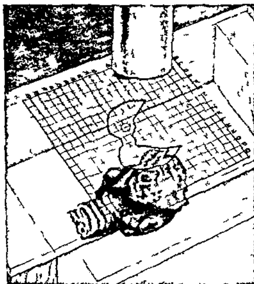


Fig 119—O tl g f d t thy d gl d t D t nal sci t ll t ount s te ed h te se t n f o- di t d ou t e t m t lly d d ec d g m ll mm t r (Courte y f *Alle H C J* d Goodw W E R d i gy 58 68-79 J ry 1952)

akin to the mechanical stage on a microscope carries the directional scintillation counter over the thyroid gland by using a system of rectangular co ordinates The counts are recorded After subtracting counts which represent the neck background a silhouette of the gland is obtained (Fig 119) Right and left lateral silhouettes are similarly obtained Formulas have been developed using the area of the frontal silhouette and the height of the gland to determine the weight of the gland In 10 cases surgical or autopsy verification of

toward hardness Microscopically connective tissue was increased and lymphoid tissue decreased Mean acinar cell height was nearly twice normal

Of the 21 patients prepared 14 of 15 who actually underwent surgery had a smooth postoperative course Three patients with slow or incomplete response one with a marked keloid tendency and two who stopped medication (one with reaction to drug) were not operated on In three patients given iodothiouracil 72 hours after a dose of radioiodine control was noted in 4 days in two and in 15 days in one Two patients receiving long term therapy have had no relapse after nine and two months of therapy

Mild leukopenia and granulocytopenia the only side effects noted occurred in one patient who received 600 mg iodothiouracil for 23 consecutive days

[I prefer to use this drug chiefly for preoperative treatment There are rapid complete remission and excellent involution of the gland in some patients but not in all Inability to predict the response is the main drawback —Ed]

Scintillation Counter as an Instrument for in Vivo Determination of Thyroid Weight is described by Herbert C Allen Jr and William E Goodwin[1] (Wadsworth Gen l Hosp Los Angeles) This device depends on emission of light from a calcium tungstate phosphor when struck by gamma radiation It is many times more sensitive to gamma radiation than the conventional Geiger Muller counter Owing to this sensitivity it has become possible in the study of thyroid function with radioactive iodine to lower the tracer dose of eight day I^{131} to harmless levels

With specially designed equipment it is possible to determine the weight of the thyroid gland in vivo knowledge essential for proper calculation of the dose of I^{131} for treating thyrotoxicosis With a wide angle scintillation counter the entire gland can be covered when the tube is placed several centimeters from the neck It is 150 times as sensitive as the end window Geiger Muller counter As little as 1 μc I^{131} can be used as a tracer dose in study of thyroid function with this instrument A directional scintillation counter has also been devised which uses varied small apertures The scintillating crystals are on the side of the tube rather than on the end It is 35 times as sensitive as the Geiger Muller counter on an

(1) R d logy 58 68 79 Jan ry 1952

A decline in the circulating lymphocytes of the blood is not uncommon after the administration of large doses of radioactive iodine Although a total dose of 800 mc in divided doses and 200 mc in a single dose have been given no grave

CLASSIFICATION OF 119 CASES OF CARCINOMA OF THE THYROID	
Follicular	27
Follicular and papillary	28
Papillary	22
Anaplastic and solid cellular	29
Anaplastic and papillary	5
Epidermoid	3
Lymphoma	3
Hurthle cell	2
Total	119

changes in the other circulating cellular elements of the blood were noted

Iodine-Deficient Human Thyroid Gland Preliminary Report. John B Stanbury Gordon L Brownell Douglas S Riggs Hector Perinetti Enrique del Castillo and Juan Itoiz[3] report results of a co operative study on endemic goiter Radioactive iodine (I^{131}) uptake by the thyroid was measured with a Geiger Muller counter using a fixed distance A wide variation in I^{131} uptake was found in 118 clinically euthyroid patients in Mendoza Argentina an area of iodine deficiency Comparison with the uptake curves of normal subjects from the Boston area showed that there may be a wide normal uptake in an area of iodine deficiency Figuring urinary ex cretion of dietary iodine (I^{1}) as virtually the complete loss the authors found that there was a good correlation between the daily excretion of stable iodide and the 48 hour accumu lation of I^{131}

Many of the clinically euthyroid patients had enlarged glands and many were iodine deficient The iodine deficient glands accumulated iodide rapidly and held it tenaciously Actually the holding is an over all phenomenon for there was evidence that iodine was being released as hormone but that it was recaptured when the hormone was broken down When 1 methyl 2 mercaptoimidazole was given as a thyroid blocking agent pronounced changes were found in the slopes of the curves of iodine utilization indicating a rapid turnover for I^{131} When thyrotrophin was given with antithyroid block

(3) J Cl E docr ol 12 191 207 F bru ry 1952

the calculated weight has been possible the average discrepancy has been ± 10% with the greatest discrepancy 25% In these cases thyroid glands ranged in weight from 10 5 to 125 Gm By use of the weight formulas it has been possible to be less conservative in dosage of I^{131} Up to 16 mc of eight day I^{131} has been used for a single initial dose without increased incidence of post therapeutic hypothyroidism A single dose accurately calculated has the advantage over the multiple dose technic in that larger and larger successive doses are avoided the gland does not become radioresistant and increased radiation of extrathyroid tissue is not necessary

[In addition to indicating the size of the thyroid the scintillation counter also shows its shape and gives some information about the physiology and consequently the nature of the disease—Ed.]

Study and Treatment of 119 Cases of Carcinoma of Thyroid with Radioactive Iodine undertaken at the Massachusetts General Hospital in the past six years is reported by Brown M Dobyns and Farahe Maloof Cases studied are classified histologically in the table

Although follicular adenocarcinomas collected more radioactive iodine than other carcinomas of the thyroid the initial isotope uptake in any of the carcinomas and their metastases was decidedly below that of the normal thyroid However removal of the normal thyroid has resulted in increased uptake of the isotope in some instances making radioactive iodine more useful particularly in follicular adenocarcinomas containing colloid After administration of thiouracil (200-400 mg every eight hours) a further increase in uptake of radioactive iodine was found in some instances

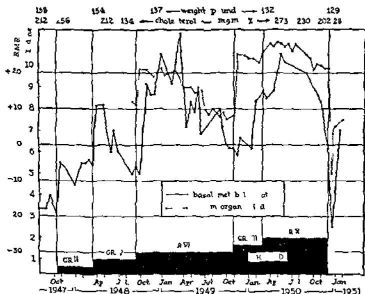
Radioactive iodine therapy was beneficial in 10 of 50 patients who had had total thyroidectomy and who had known metastatic lesions left Of the 10 6 had follicular adenocarcinoma 3 mixed follicular and papillary adenocarcinoma and 1 papillary adenocarcinoma In a few patients with incapacitating metastatic disease rate of growth had been curtailed and biopsies of some lesions showed destruction by radiation

Uptake in rapidly growing anaplastic lesions has been insufficient for therapy Some papillary lesions however have a follicular component and will take up appreciable amounts of radioactive iodine

(2) J Cl n E doc 1 11 1323 1360 N mbe 1951

administered The uptake of a number of other patients who had been receiving constant doses of thyroid for several years was also measured as was that in a number of patients in control periods and early weeks of thyroid therapy

Most patients receiving 2 gr thyroid daily showed an early rise in metabolic rate followed by a gradual decline in four to six months to or toward normal level With 4 gr



F g 120—Re p n f thy o d p c ous m p t t 58 to thy d She had m ld to ymptom t ta t f g 6 d g per od b t th y l t b d d At d f g 10 p d sh w found t h or f the t m h (Court y f J h t M W *et al* A I t M d 35 1008 1022 N mbe 1951)

daily BMR and serum protein precipitable iodine rose to higher levels and in a few instances there were toxic symp toms On continued therapy at this level both values fell gradually with one exception but did not reach initial levels On daily ingestion of 6 gr or more both levels rose and mild toxic symptoms were frequent (Fig 120) they gradually declined but tended to become stabilized well above the con trol level Most euthyroid patients acquired a tolerance to large amounts of thyroid but there was individual variation

ing agents it was clear that the thyrotrophin had a stimulating effect on the secretory function of the thyroid gland Pain, tenderness and swelling of the gland occurred in each of the six patients to whom thyrotrophin was given This subsided after two or three days The cause is not clear The thyrotrophin effect is interpreted to mean that the glands of these patients were not under maximal stimulation from endogenous thyrotrophin

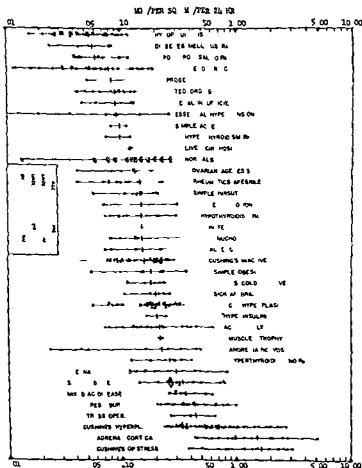
When daily supplemental rations of iodide were given to patients with initially high thyroid uptakes of I^{131} it was found that the accumulations of I^{131} in subsequent tests were persistently high None of the patients had symptoms suggesting thyrotoxicosis and the gland did not appear to change in size The authors believe that these findings probably represent storage of iodine

A group of patients with high I^{131} uptake were given desiccated thyroid In most the uptake was depressed the degree varying with the amount of thyroid given

Effect of Prolonged Administration of Thyroid was investigated by MacAllister W Johnston A H Squires and R F Farquharson[4] (*Toronto*) Many of the patients observed were obese others had mild psychoneurosis and were glad to receive attention They had either normal or slightly decreased BMR and serum cholesterol levels within normal range None had symptoms of hypothyroidism Sixteen patients started on 2 gr Canadian Standard thyroid daily At intervals of many months dosage was increased in 2 gr increments to a maximum of 10 gr daily For various reasons some patients dropped out of the series at one stage or another Only two carried through to the 10 gr dosage another reached the 8 gr level and many reached the 4 and fewer the 6 gr level

The clinical condition of the patients was followed carefully On completion of therapy the 24 hour radioactive iodine uptake of the thyroid gland was measured at weekly intervals A small test dose of 10 20 μc diluted with a small quantity of distilled water was injected intravenously and the uptake measured by a lead shielded Geiger Muller counter tube at 6 in from the center point of the isthmus of the thyroid and expressed as percentage of total dose

(4) A n. Int. M d 35 1008 10 2 November 1951



F g 121 —Ob t on ry ort t 3 outp t f p t t w th c 1 t E h plot p se t d d l l cc di g to l g thm cale. T tal p f l g t tal g of l obt d f p t nt w th ch d gn s. oh t rt l l s g h h tal l e nd t g f f (Cou t y f Talb t N B r l J Cl E doc nol 11 1224 1236 N embe 1951)

The previously noted tendency of hypoadrenocortical hypopituitary and hypothyroid patients to have a subnormal corticosteroid output was confirmed In addition suggestively low mean values were obtained for a small group with con trolled diabetes mellitus The mean in idiopathic osteoporosis

in the degree of tolerance obtained The tolerance developed on a given large dose was associated with a gradual decrease in serum protein precipitable iodine and BMR Ingestion of excessive amounts of thyroid over a long period does not appear to affect the gland permanently The depression is reversible and after cessation of thyroid therapy normal activity is soon regained The internal secretion of the thyroid gland may be greatly decreased and the gland reduced in activity and put at rest by the presence in the body of excessive amounts of its specific hormone

Thyroid uptake of radioiodine by patients who have taken moderately large doses of thyroid over long periods lies in the anterior pituitary insufficiency range prolonged ingestion of smaller amounts leaves the uptake in the normal range and ingestion of larger amounts lowers the uptake to myxedema levels These observations lend support to the idea that the decreased activity of the thyroid gland is due to decreased secretion of the thyrotrophic hormone by the anterior pituitary

[Important observations showing the amount of refractoriness to desiccated thyroid that may be acquired and the relative thyroid insufficiency on stopping therapy Athyreotic subjects do not develop refractoriness —Ed]

ADRENAL GLANDS

Further Observations on Urinary Excretion of Water Soluble Corticosteroids by Normal and Abnormal Subjects N B Talbot M S Wood J Worcester E Christo A M Campbell and A S Zygmuntowicz[5] (Harvard Univ) found the daily urinary output of corticosteroids in healthy unstressed persons to be essentially the same at all ages (average 0 132 mg./sq m body surface) The mean in 18 children under 7 was 0 101 in 26 aged 7 14 was 0 126 and in 31 persons 15 or older 0 143 mg /sq m /day Extension of this method of expressing measurements to patients with various conditions permits easy comparison of results obtained on subjects of different sizes with the same disease Figure 121 shows 640 measurements obtained on 315 patients falling into 38 diagnostic categories

(5) J Clin Endocrin 11 1224-1236 November 1951

steroid excretion were consistent with the therapeutic efficiency of the doses used

Purified corticotrophin appeared to be about twice as effective clinically as would be expected from the animal assay This is probably related to the increased stability of purified corticotrophin in body fluids This preparation is 150 times as effective clinically as standard corticotrophin and at least 250 times as effective (on a weight basis) as cortisone Experience with it indicates that newer preparations of corticotrophin will require clinical evaluation to determine dosage and frequency of administration

ACTH and Cortical Steroids in Postpartum Plasma. Louis W Granirer[7] (Jamaica N Y) presents a preliminary report of an investigation to examine the mode of action of postpartum plasma in rheumatoid arthritis

METHOD—Twelve Sprague Dawley male rats weighing 120 160 Gm were hypophysectomized by the parapharyngeal approach. After 21 27 hours they were anesthetized with ether and the left adrenal was removed Six rats were given postpartum plasma intravenously and six a standard ACTH solution One hour later the right adrenal was removed The response was expressed as the difference in concentration of ascorbic acid between right and left adrenals The ascorbic acid depletion produced by the test material was compared with that produced by the ACTH preparation Activity of the test material was expressed as percentage of standard

Tests were first made with fresh pooled postpartum plasma taken from 10 mothers 24 hours after delivery Results indicated that there is a quantitative ratio between micrograms of ACTH injected and milligrams of adrenal ascorbic acid depletion produced Each cubic centimeter of test material contained 1 8 μg ACTH by potency The plasma assayed 112% of standard A control group of specimens of fresh pooled plasma from females failed to produce any ascorbic acid depletion Pooled postpartum plasma refrigerated for five weeks contained 0 56 μg ACTH/cc eight week old postpartum plasma showed no ACTH activity Adrenal cortical hormones 20-40 μg/cc were detected by paper chromatography in all postpartum plasma specimens one to four months old

It is evident that in the hypophysectomized rat *fresh* pooled postpartum plasma will deplete the ascorbic acid content of the adrenal glands a change accepted as indica

(7) N w Y k J M d. 51 2767 2769 D c. 1 1951

was slightly below normal a finding of doubtful significance Mean values in essential hypertension, ovarian agenesis quiescent rheumatic fever simple nonendocrine hirsutism adequately treated hypothyroidism eunuchoidism and allergy fell within the normal range

Abnormally high values were obtained in pathologic hyperadrenocorticism due to adrenocortical cancer evidenced clinically by virilism or Cushing s syndrome Patients with bilateral adrenocortical hyperplasia who showed only signs of virilism had a slightly to moderately elevated mean value of about 0 2 whereas those who displayed manifestations of Cushing s syndrome had a notably elevated mean output of 0 7 mg /sq m /day Overlap between the values found in adrenocortical hyperplasia as compared to cancer was great so that corticosteroids measurements cannot per se be relied on to distinguish between the two

Patients with physiologic hyperadrenocorticism occasioned by the stress of various conditions including febrile illnesses operation and burn excreted corticosteroids at rates comparable to those in pathologic hyperadrenocorticism

Data obtained in over 1 400 corticosteroids measurements support the view that this determination is a reliable index of adrenal corticosteroid production

[*This is the most extensive study of its type The test is helpful in evaluating adrenal function* —*Ed*]

Enhanced Clinical Effectiveness of Purified Corticotrophin. M S Raben I N Rosenberg V W Westermeyer and E B Astwood[6] (New England Center Hosp Boston) used material which had been purified by the oxycellulose method and contained 80 units/mg by bioassay It was given subcutaneously every 8 hours in aqueous solution or every 24 or 48 hours in gelatin solution or as a suspension in sesame oil The gelatin solution prolonged the action of corticotrophin best and reduced the daily dose below that required for injections of aqueous solution at eight hour intervals Before the augmented clinical potency of this material was realized evidence of excessive dosage was easily obtained There was no qualitative difference between the therapeutic or overdosage effects of the pure and the impure preparations The fall of erythrocyte sedimentation rate and rise in 17 keto

(6) J A M A 148 844 845 Mr 8 1952

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( ) N w Y k J Med. 51 767 2769 D 1 1951

tive of ACTH activity Apparently ACTH disappears from pooled postpartum plasma within six to eight weeks but the plasma contains other corticoids as yet unidentified which may stimulate ACTH secretion in the intact animal

[It has been known for several years that toward the end of pregnancy a great increase in urine content of glucosteroids is demonstrable Their source is most probably the placenta —Ed]

ACTH and Cortisone vs Salicylates Salicylate therapy has many biologic effects similar to those of cortisone and ACTH These and the points of difference are tabulated by H F Hailman[8] (Kalamazoo Mich) Similarities include (1) fall in adrenal ascorbic acid (2) decrease in circulating eosinophils (after six but not after four hours with salicylates) (3) increase in urinary 17 ketosteroids (4) clinical improvement in rheumatic fever and rheumatoid arthritis (5) prevention (cortisone) or abatement (aspirin) of joint swelling due to intra articular injections of irritant substances (6) reduction of febrile reactions (7) alleviation of joint pain (8) decrease in sedimentation rate in rheumatic fever and rheumatoid arthritis (9) increase in urinary excretion of uric acid (10) production of negative nitrogen balance (11) inhibition of spreading effect of hyaluronidase (12) inhibition or reduction of skin sensitivity reactions (13) inhibition of serum vascular disease (14) diminution of ocular inflammatory changes (15) production of Cushing's syndrome or portions thereof (16) inhibition or reduction of anaphylactic shock However some reports indicate that ACTH and cortisone differ from salicylates in that the former may have no effect in anaphylactic shock in guinea pigs ACTH and cortisone have no true analgesic effect some believe that aspirin has Cortisone increases liver glycogen whereas salicylates cause a fall in liver glycogen and reduce glycosuria in diabetic rats It may be that salicylates operate through the pituitary adrenal mechanism

Effect of ACTH on Erythrocyte Sedimentation Rate and Plasma Fibrinogen and Serum Protein Levels in Normal Persons Of the various constituents of plasma fibrinogen is believed to be the most important single factor causing a raised erythrocyte sedimentation rate in acute disease A parallel reduction in sedimentation rate and plasma fibrinogen has been demonstrated in patients with rheumatic fever treated with

(8) J Clin Endoc 1 12 454-457 April 1952

ACTH and cortisone (Fig 122*A*) Since a similar parallelism has been demonstrated in a patient with carcinomatosis treated with ACTH (*B*) George R Fearnley and Joseph J Bunim[9] (New York Univ) concluded that the fall in sedimentation rate could result from a nonspecific effect of the hormones To investigate this further the sedimentation rate plasma fibrinogen and serum protein levels were determined in seven healthy adults aged 20 30 Two were women Single

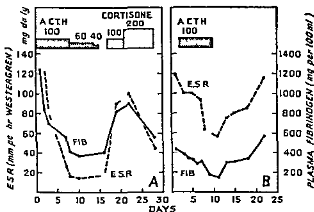


Fig 12 —Pl m fib g l l d yth ocyt d m t t t d g t eatment w th ACTH d ortı (*A*) heumat fever d (*B*) ca mato- (C t y f F l y G R d B m J J L t 2 1113 1116 D 15 1951)

doses of ACTH (usually 40 mg) were given to six persons the seventh received four separate doses of 40 mg

The plasma fibrinogen level fell in four did not change in one and rose in two There was no remarkable change in serum albumin serum globulin levels were inconstant Only one test showed a significant fall in sedimentation rate this patient had the greatest fall in plasma fibrinogen

These results and those in animals suggest that the effects of corticotrophin and stressing agents on plasma fibrinogen are not simple In disease plasma fibrinogen levels will be subject to two opposing forces inflammation as an elevator and hormonal action as a depressor It is impossible to tell whether there is active inflammation in the heart in rheumatic

(9) La t 2 1113 1116 D 15 1951

fever when the sedimentation rate has been brought to normal by ACTH or cortisone Until more information is available it seems best not to consider the normal sedimentation rate as a reliable index of absence of rheumatic fever in patients treated with these hormones

Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone II Effects of Cortisone on Sexual and Somatic Development, with Hypothesis Concerning Mechanism of Feminization Lawson Wilkins John F Crigler Jr Samuel H Silverman Lytt I Gardner and Claude J Migeon[1] (Johns Hopkins Univ) treated six female pseudo hermaphrodites aged 8½ 18½ continuously with cortisone for 5 17 months In all the breasts promptly developed and vaginal smears showed estrinization Three patients menstruated regularly There was an unquestionable decrease of hirsutism in all patients to a spectacular degree in two Associated hypertension present in two was notably decreased To obtain the most satisfactory results it is essential to give the minimal amount of cortisone necessary to maintain excretion of 17 ketosteroids below 8 mg/day in the older patients since androgenic manifestations recurred when larger amounts of ketosteroid were excreted

In one infant 25 mg intramuscular cortisone daily inhibited growth and osseous development but 5 mg was sufficient to suppress excessive androgen secretion without inhibiting normal growth During childhood it is advisable to follow both urinary 17 ketosteroid values and rates of growth and osseous development as guides to treatment The minimal effective dose of cortisone and the level at which the urinary 17 ketosteroids should be maintained must be determined in each case

Two boys with macrogenitosomia praecox were treated for long periods In one 6 years and 10 months old cortisone not only suppressed the excessive secretion of adrenal androgen responsible for rapid growth and virilization but at the same time led to adolescent development and growth of the testes In the second with associated hypertension cardiac failure followed excessive doses of cortisone but 12 5 mg cortisone daily controlled hypertension and caused surprising improvement in the cardiac condition and general health

(1) J Cl E doc in I 12 277 95 M h 195

Cortisone probably inhibits secretion of ACTH by the pituitary and secretion of adrenal androgen and estrogen decreases notably This permits secretion of pituitary gonado trophins causing maturation of the ovary and secretion of estrogen The ovarian estrogen is no longer antagonized by excessive adrenal androgen and normal secondary sex develop ment results The normal pituitary-ovarian mechanism leads eventually to the establishment of menstrual cycles with ovulation corpus luteum formation and progesterone secre tion A similar mechanism in the male may be expected to lead to maturation of the testes with spermatogenesis

Subtotal Adrenalectomy for Cushing's Syndrome Prelim inary Report of 29 Cases in which surgical exploration failed to reveal a functioning tumor of the adrenal cortex is pre sented by James T Priestley Randall G Sprague Waltman Walters and Robert M Salassa (Mayo Clinic) All patients had clinical and laboratory evidence of Cushing s disease and most had the condition in severe form Six patients were males With tumor on one side the contralateral adrenal obviously should not be removed At first the authors ex plored both glands before either was resected With increas ing experience the plan of treatment was based on the ap pearance of the first gland exposed because it has been con sistently noted that with a functioning tumor on one side the contralateral gland appears atrophic whereas in so called adrenal cortical hyperplasia the appearance of both adrenals is virtually identical and neither is atrophic In the latter case a subtotal adrenalectomy (90%) was performed on one side and a total adrenalectomy on the other some time later

In the first 20 cases aqueous adrenal cortical extract was used in both preoperative and postoperative care 40 cc extract was administered intramuscularly the evening before and another 40 cc just before the operation Convalescence after resection of the first adrenal was usually uneventful If no functioning tumor was found and a subtotal resection of the first adrenal was done usually little or no additional extract was required Before resection of the second adrenal the patient was prepared as before the first operation In addition 20 50 cc aqueous adrenal cortical extract was given in 1 L saline during the procedure Intramuscular and intra

(2) A S g 134 464 475 S pt mb 1951

fever when the sedimentation rate has been brought to normal by ACTH or cortisone Until more information is available it seems best not to consider the normal sedimentation rate as a reliable index of absence of rheumatic fever in patients treated with these hormones

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(1) J Cl n F doc n l 12 7 95 M ch 1952

[Adrenalectomy constitutes the best treatment in severe cases Roentgen therapy to the pituitary and testosterone are satisfactory in some less severe cases —Ed]

PITUITARY GLAND

Neural Control of Pituitary Gland II. Adenohypophysis with Special Reference to Secretion of ACTH Experiments reported by G W Harris[3] (Cambridge) indicate that the normal stimulus to anterior pituitary activity is derived from the hypothalamus by way of a portal blood system arising in the median eminence and carrying blood to the tuber cinereum Activity of the adenohypophysis is seriously impaired or stops if it is so separated from the hypothalamus that the portal vessels cannot reach it The basic output of ACTH depends largely on an intact hypothalamic hypophyseal relation (via the portal vessels) Under optimal conditions the fine control of ACTH is probably exerted by the blood level of adrenal cortical hormones The epinephrine blood content also seems able to modify ACTH output In both instances this effect appears to be by way of the hypothalamus and not by direct action on anterior pituitary cells Stress may increase output of ACTH by changing levels of adrenal hormones or by acting on higher neural centers which in turn influence the hypothalamus the latter can then modify the output of the adenohypophysis Similar hypothalamic controls are postulated for control of gonadotrophic hormones from the adenohypophysis

[In severe stress stimuli go to the region of paraventricular nuclei then travel down the spinal cord and through the sympathetics to the adrenal medulla With increased release of epinephrine the anterior pituitary is stimulated directly and presumably indirectly from the hypothalamus to increased secretion of ACTH With increased release of adrenal cortico d ACTH release is inhibited —Ed]

Antidiuretic Hormone Studies in Patients Presenting Edema are reported by Mary Dochios and Leonard S Dreifus[4] (Hahnemann Med College) Of 16 patients with clinical edema 12 had congestive heart failure 2 cirrhosis of the liver and 2 controlled Addison s disease All were maintained on a 1 Gm sodium chloride diet and diuretics were withheld during course of study Results indicate that the esti

(3) B t M J 2 627 634 S pt 15 1951
(4) Am J M Sc 222 538 543 Novembe 1951

venous administrations of extract were continued for several days after operation the exact quantity used being determined by the patient s clinical status With this method the immediate shocklike reaction which occurs within the first 24 72 hours and closely resembles severe acute adrenal cortical insufficiency was averted Intravenous administration of extract was usually discontinued after a few days and then the quantity of extract administered intramuscularly gradually reduced After resection of the second adrenal the patient usually did well for 10 20 days and then a delayed reaction characterized by anorexia increasing nausea and finally vomiting developed Weakness fever and tachycardia were usually present but the blood pressure as a rule did not fall to the low levels common in acute adrenal insufficiency Some patients had abdominal pain and some had muscular and articular symptoms resembling fibrositis and periarthritis Large amounts of aqueous adrenal cortical extract 100 200 cc daily together with normal saline did not relieve this condition which sometimes persisted four to six weeks

Of the 29 patients 6 died 3 of them had stormy postoperative courses which did not respond to large doses of aqueous adrenal cortical extract Autopsy in one of the three revealed acute and chronic hemorrhagic pancreatitis in the other two fat necrosis in the tail of the pancreas Three patients were operated on too recently to permit evaluation In one patient who did not improve considerable adrenal tissue may have been left In 19 remissions were excellent Manifestations of the syndrome regressed over several weeks or months The characteristic habitus gradually disappeared plethora and ecchymosis faded the skin became thicker and purple striae lost their color In many patients hypertension disappeared and blood pressure returned to normal but in others residual mild hypertension persisted Menses became normal and three patients have subsequently become pregnant Of the 19 patients 3 have had recurrences of the signs and symptoms of Cushing s syndrome after remissions lasting three years two years and nine months Three had chronic adrenal cortical insufficiency and required daily replacement therapy Though typical addisonian pigmentation occurred in these three there was similar pigmentation in others with no clinical or laboratory evidence of adrenal cortical insufficiency

terior pituitary extracts and absence of such activity in control extracts No relation was found between hormone content and sex but striking differences were apparent when material was grouped according to disease

Glands from 18 patients with no abnormalities of water metabolism gave uniform activity and comprised the nor mal group Causes of death in this group were malignancy tuberculosis sepsis meningitis abortion leukemia and gas tric ulcer A significantly higher antidiuretic activity was found in cases of renal and essential hypertension cirrhosis with ascites cardiac failure with edema diabetes mellitus eclampsia and Addison s disease Pronounced reduction of antidiuretic potency was found in a case of diabetes in sipidus in which the posterior lobe was replaced by tuber culous granulation and in one of hemochromatosis in which the posterior lobe was strongly pigmented

[The quantity of antidiuretic hormone is increased in the urine and pituitary of patients with edema associated with a variety of diseases its main stimulus apparently is hyperosmosis of the blood. Adrenal corticoids antagonize this hormone —Ed]

mate of the amount of edema correlated with the amount of urinary antidiuretic hormone the latter being proportionately higher in those with more edema and less urinary output Serum sodium and potassium levels remained within normal limits irrespective of the clinical status The low salt diet had not affected the serum sodium levels in most but may have been responsible for the low values of serum chlorides In four patients whose 17 ketosteroid excretion was determined values were low when antidiuretic hormone titers were high All patients with clinical edema also responded abnormally to the Kepler Power water test This indicates some derangement of adrenal cortical function and may be the result of posterior adrenal imbalance due to a primary derangement of adrenal cortical activity

An antagonistic action apparently exists between the posterior pituitary and adrenal cortex in controlling the renal excretion of water Untreated patients maintained high antidiuretic hormone and low 17 ketosteroid levels normal water diuresis was absent However enough adrenal cortical function may remain in the patients with congestive heart failure to maintain normal serum sodium levels but not enough compound E fractions to maintain normal excretion of water In contrast addisonian patients have a loss of both sodium and water because of a total adrenal cortical insufficiency It is inferred that normal salt and water metabolism may be restored in patients with clinical edema by administration of cortical like substances

Antidiuretic Hormone of Posterior Lobe of Human Hypophysis was quantitatively studied in postmortem material from 58 subjects including those with disease with known disturbances of water metabolism by Cesare Cavallero and Marco Zanchi[1] (Univ of Milan)

Method —Extracts were prepared by grinding freshly dissected posterior pituitary lobes in a mortar with 0 9% NaCl solution using 1 ml saline/mg of gland The extract was immediately injected into rats after fasting for 12 hours dose was 0 5 ml extract/100 Gm rat Control experiments were made with the same volume of normal saline only and with extracts of cerebral and cerebellar cortex and pineal body The output of urine was calculated as percentage of water administered

Results demonstrated a high antidiuretic effect of pos

(1) J P th. & Bact. 63 249-257 April, 1951

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